Los **trastornos mentales** son más frecuentes en las mujeres que en los hombres, hecho que se respalda con el artículo clásico de Weissman, en el cual se realiza una comparación de diferentes regiones y se observó que la **prevalencia de depresión era casi el doble en mujeres que en hombres**.

La epidemiología sobre esta materia requiere una renovación en México, puesto que –en el 2003– se llevó a cabo la última Encuesta Nacional de Epidemiología Psiquiátrica; sin embargo, desde ese momento se identificó que, tanto en los **trastornos afectivos** (incluyendo la depresión) como en los ansiosos, la prevalencia es mayor en mujeres que en hombres. Por otro lado, para el consumo de sustancias adictivas, se estableció que la frecuencia es mayor en hombres que en mujeres.

## Factores predisponentes para padecer depresión

Entre los **factores de riesgo** más importantes se encuentra el trabajo en el hogar, un bajo nivel socioeconómico, el desempleo (particularmente en hombres), el aislamiento social, tener problemas legales, experiencias traumáticas y el consumo concomitante de sustancias adictivas; no obstante, **el mayor es ser mujer**, población en la que puede presentarse a edades tempranas, lo que incrementa el riesgo de cronicidad. Asimismo, tienden a tener más síntomas y expresar una peor calidad de vida. La principal causa de esto son las **hormonas**, ya que afectan las emociones y el estado de ánimo.

## Síndrome premenstrual y trastorno disfórico premenstrual

Estos **trastornos son similares**. Presentan síntomas que **comienzan desde 7 a 10 días previos a la menstruación** y persisten durante los primeros días de la misma. Generalmente, estos son físicos y pueden incluir **edema, cefalea, sensibilidad en los senos, acné, alteraciones digestivas, cambios en la alimentación y en el sueño**. A nivel emocional, el **síndrome premenstrual (SPM)** presenta irritabilidad,

mientras que en el **trastorno disfórico premenstrual (TDPM)** –siendo una extensión grave e incapacitante del primero– la irritabilidad se exacerba y se acompaña de tristeza, desesperanza, ansiedad e ira. Esto ocurre de manera cíclica, comúnmente, en mujeres jóvenes.

Los **síntomas pueden asemejarse a trastornos depresivos y de ansiedad**, por lo que es importante hacer un diagnóstico diferencial con ambos padecimientos, aunque en muchas ocasiones se manifiestan conjuntamente. Por ejemplo, la paciente puede tener un trastorno depresivo mayor más un TDPM, donde el último se asociará con síntomas físicos relacionados al ciclo menstrual.

El **tratamiento**, principalmente, estará dirigido a **prevenir o minimizar los síntomas**, de manera que los cambios en el estilo de vida son importantes, como: hacer ejercicio aeróbico, reducir el consumo de cafeína, evitar el alcohol, no fumar, dormir adecuadamente, hacer técnicas de relajación y respiración. También pueden emplearse **suplementos nutricionales** (como calcio, vitamina B y magnesio), **pastillas anticonceptivas** (tratamiento hormonal) y **antidepresivos con inhibidores selectivos de la recaptura de serotonina** (como sertralina y fluoxetina). Los medicamentos pueden prescribirse los 7 días previos al ciclo menstrual o continuamente cuando existe algún trastorno depresivo o de ansiedad.

## Infertilidad

En algunas ocasiones, las mujeres tienen el deseo de ser madres, de tal manera que el no lograrlo puede ser un factor estresor importante a nivel personal y de pareja. Igualmente, puede generar mucha inseguridad, así como pensamientos de culpa. La revisión de la literatura demuestra que la **ansiedad, depresión y disminución de la calidad de vida prevalece en las experiencias de infertilidad**, tanto en la población femenina como en la masculina sin importar de dónde provenga la persona o de qué cultura sea.

El proceso de fertilidad conlleva un **desgaste físico para la mujer**, ya que tiene que aplicarse tratamientos hormonales constantemente sin realizarse estudios de laboratorio; un **desgaste emocional y mental**, por el proceso que involucra

llevar a cabo el ciclo de fertilización *in vitro* en repetidas ocasiones sin éxito en resultar embarazada, y un **desgaste económico alto**, por lo costosos que son estos procedimientos.

## Depresión perinatal

En términos objetivos, **tener un bebé es un factor estresante**. Esto se debe a que conlleva la adquisición de nuevas responsabilidades y el "abandono" de otras, la falta de sueño y tiempo, tanto para la persona como para la pareja, por ende, todos estos son factores de riesgo para presentar **depresión perinatal**.

### Definición

Anteriormente, la **depresión en el embarazo** se conocía como *depresión posparto*, es decir, después del nacimiento del bebé; pese a esto, hay literatura que menciona que el 50% de los episodios depresivos comienzan antes del parto, de modo que el término se cambió a *depresión perinatal*, la cual hace referencia a aquella que **ocurre antes (en procesos de infertilidad o propiamente al embarazarse), durante (comprende los 9 meses de gestación) y después (hasta el primer año de vida del bebé) del embarazo.** Los síntomas de esta enfermedad pueden ir de leves a graves e, incluso, poner en peligro la salud de la madre y el bebé.

### Diagnóstico

De acuerdo con el DSM-5, los criterios de diagnóstico incluyen dos puntos obligatorios, los cuales son el **tiempo** (cómo se ha sentido la mujer en las últimas dos semanas) y la **presencia de tristeza** (la mayor parte del día a diario) junto con **anhedonia** (incapacidad para disfrutar plenamente la vida o falta de interés por las cosas que le gustan e interesan) y, por otro lado, la presencia de 4 de los siguientes 7 criterios: **alteraciones en el apetito** (al alta o a la baja), **alteraciones en el sueño** (desde insomnio hasta hipersomnia), **lentitud psicomotriz** (física y mentalmente), **sentirse fatigada o con poca energía, sentimiento de valer menos que las demás personas, fallas en la atención y concentración y sentimiento de que no vale la pena vivir.**

Características clínicas

Las características clínicas de la depresión perinatal son iguales a las de depresión y se identifican conforme a los criterios mencionados; no obstante, pueden estar acompañados de **ansiedad, indecisión en los cuidados para el bebé, preocupaciones excesivas, temor de daño involuntario o a quedarse sola con él.** Asimismo, la mujer puede presentar pensamientos sobre que es mala madre y tener sentimientos de culpa o rechazo hacia el bebé.

Las consecuencias de lo anterior afectarán a la madre, el vínculo materno-infantil y al bebé. Para la primera, serán control médico escaso, uso concomitante de sustancias adictivas en la etapa posparto, **mayor riesgo de aborto, dificultad en el parto, hipertensión o hemorragia en el embarazo y en el posparto** e, incluso, suicidio; con respecto al segundo, habrá **dificultades en la lactancia**, en el reconocimiento y la respuesta a las necesidades del lactante, así como una carencia en el cuidado que puede llevar a negligencia; por último, en el tercero, puede generar **restricción en el crecimiento intrauterino, bajo peso al nacer, parto prematuro,** mayor riesgo de ingresar a terapia intensiva, alteraciones del neurodesarrollo, apego inseguro e incremento en el riesgo de padecer enfermedades mentales a lo largo de la vida.

Tratamiento

Este dependerá de la severidad de los síntomas y de cómo alteran la funcionalidad. En el caso de que estos sean leves, pueden emplearse **estrategias psicosociales**, como técnicas de relajación y respiración; si son moderados, debe comenzarse con **psicoterapia** (por lo general, terapia cognitivo conductual) y realizar una evaluación médica con un psiquiatra; en casos graves, el tratamiento requerirá de **intervenciones farmacológicas**, siendo los inhibidores selectivos de la recaptura de serotonina los de primera elección.

Las guías internacionales establecen esta clasificación (canadiense y americana): entre los inhibidores selectivos de la recaptura de serotonina se encuentran medicamentos como **citalopram, fluoxetina, fluvoxamina, paroxetina y sertralina**, mientras que en los antidepresivos duales se hallan la **desvenlafaxina,**

**duloxetina y venlafaxina**. Es importante mencionar que existen riesgos potenciales asociados a la depresión no tratada, así como al uso de antidepresivos en esta etapa de la vida. Al no tratar, pueden desarrollarse alteraciones conductuales, embarazo a pretérmino, bajo peso al nacer y trastornos en el neurodesarrollo del bebé. Los principales riesgos de tratar comprenden síndrome de pobre adaptación al nacer y aumento en el riesgo de ingreso a terapia intensiva.

Es **importante tomar en cuenta el deseo de embarazo** en las pacientes en edad reproductiva si se iniciará un tratamiento antidepresivo. De igual manera, deben evaluarse los síntomas y decidir si se suspende el tratamiento (en caso de que ya se le esté administrando) o continuarlo, puesto que los antidepresivos pueden producir malformaciones congénitas cardíacas y de tubo neural, también aumentan el riesgo de aborto espontáneo y pueden producir hipertensión pulmonar en el feto.

Si se decide **iniciar el tratamiento durante el embarazo**, el segundo trimestre y la primera mitad del tercero son los periodos más seguros. Si se realiza el diagnóstico antes de este momento, debe comenzarse con psicoterapia y esperar el momento oportuno para disminuir el riesgo de malformaciones congénitas. La prescripción debe empezar con dosis bajas para asegurar la tolerabilidad y alcanzar una dosis mínima efectiva en, aproximadamente, una semana. Posteriormente, deberá ajustarse la dosis según la respuesta haciendo evaluaciones constantes de la misma, tomando en cuenta que el tratamiento durará mínimo seis meses.

El **uso de benzodiacepinas durante el embarazo debe ser limitado**, ya que su administración en el primer trimestre puede contribuir al desarrollo de labio y paladar hendido y alteraciones a nivel del tracto gastrointestinal, mientras que en el tercer trimestre puede generar mayor riesgo de parto prematuro, bajo peso al nacer, síndrome de abstinencia y crisis convulsivas.

Estudios sobre depresión perinatal en México

Se realizó un estudio en 210 mujeres, donde se evaluó la presencia de síntomas depresivos durante tres tiempos conforme a los criterios diagnósticos. Los tres periodos fueron: tercer trimestre de embarazo, seis semanas y seis meses posparto. La prevalencia de los síntomas en el primer periodo fue del 16%, en el segundo del 17% y en el último del 20%, resultados que no solo indican la permanencia de los mismos, sino la posibilidad de su aumento. Al hablar de la **depresión clínica**, donde se cumplen todos los criterios, el valor en el primer periodo fue del 9%, aumentó en el segundo a 13.8% y permaneció estable en el tercero con 13.3%, lo que resalta la importancia de la evaluación a lo largo de todo el proceso.

En el mismo estudio se encontraron distintos **factores predisponentes para padecer depresión perinatal**, como: **edad joven** (relacionado con las altas tasas de embarazo adolescente), **menor escolaridad, inestabilidad de pareja, desempleo y menor nivel socioeconómico**. Otros factores que se encontraron fueron la presencia de antecedentes de depresión perinatal o enfermedad mental previa (misma que se agravaría en esta etapa), consumo de sustancias adictivas, antecedentes de eventos traumáticos en la infancia, sufrir violencia, poco apoyo social y el padecimiento de enfermedades médicas.

Otro estudio realizado por la doctora Lara, en el cual entrevistaron a 41 mujeres en el tercer trimestre de embarazo y 30 mujeres en la cuarta y sexta semana posparto, se determinó que la mayoría conocía el término “depresión posparto” y estaba atribuida a no poder enfrentar los nuevos retos que implicaba el nacimiento de un bebé, en otras palabras, los cambios emocionales, hormonales y la falta de apoyos sociales. Por otra parte, la mayoría de las entrevistadas consideró que era difícil externar su sentir, lo que indica que muchas mujeres viven este proceso de manera silenciosa por la tendencia social de asociar este evento a motivos de felicidad o entusiasmo.

También se reveló que la **psicoterapia individual** era el tratamiento con mayor aceptación; sin embargo, se presentaban barreras para llevarlo a cabo entre las cuales se encontraban la falta de tiempo, la realización de trámites

institucionales, la imposibilidad de pagarlo y la carencia de cuidado de los hijos mientras este se realizaba.

Baby blues

No todas las mujeres presentan depresión posparto, pero un alto porcentaje (hasta un 84%) padecerá "baby blues", que se define como un **conjunto de síntomas leves que se manifiestan después del nacimiento del bebé**. Los síntomas que lo caracterizan son: **sensibilidad, cambios de humor, irritabilidad, preocupación, ansiedad, insomnio, falta de concentración y fatiga**; serán leves y durarán entre una o hasta dos semanas y remiten por sí solos. Este se asocia a cambios hormonales que ocurren rápidamente cuando nace el bebé. Puede complicarse, de manera que evoluciona a un trastorno depresivo mayor, como lo es la depresión perinatal.

Lactancia materna

Este proceso es beneficioso, tanto para la madre como para el bebé, puesto que **facilita el vínculo materno-infantil**, reduce el riesgo de la depresión postparto al mejorar la calidad del sueño de la madre, reducir los niveles de estrés y ansiedad, también el riesgo de maltrato hacia el bebé y favoreciendo el desarrollo cerebral del mismo. Esto último realza la importancia de la promoción de la lactancia por parte del personal de salud.

Únicamente se pueden utilizar dos **antidepresivos en este periodo: paroxetina y sertralina**. Esta última, puede emplearse a lo largo del periodo perinatal, ya que es altamente segura, hecho que se demuestra en la baja probabilidad de que el bebé tenga concentraciones cuantificables del fármaco, asimismo, en el poco registró de eventos adversos.

## Menopausia

Es causada por la **pérdida de la función folicular de los ovarios y la disminución de los niveles de estrógenos en la sangre**. El **periodo perimenopaúsico** es aquel en el que **todavía se presenta el ciclo menstrual, pero es irregular**. A lo largo de esta etapa hay síntomas como incremento en el calor corporal, sudoración,

dificultad para dormir y cambios de humor. En la **menopausia**, ya propiamente dicha, la última menstruación se presentó hace un año (cesó). Estas mujeres pueden presentar dispareunia, problemas urinarios, insomnio y emociones exacerbadas.

Durante esta transición, se ha observado que hay tasas más altas de trastornos depresivos que cursan con mayores síntomas por los bajos niveles de estrógenos. La **depresión** puede llegar a ser más grave en estas mujeres, por lo que es resistente al tratamiento antidepresivo convencional y deberá combinarse con tratamiento hormonal. Los **factores de riesgo** incluyen a las poblaciones de raza blanca, de menor nivel educativo, con diagnóstico previo o tratamiento de depresión o ansiedad, aquellas que han vivido eventos traumáticos, con alteraciones del sueño y aquellas con problemas familiares o de violencia.

El **tratamiento no farmacológico** incluye técnicas, como acupuntura e hipnosis; sin embargo, lo fundamental es el **cambio en el estilo de vida** a través de la ejercitación, una alimentación sana, dormir las horas necesarias, bajar o suspender el consumo de tabaco e ingesta de bebidas frías para evitar el calor corporal. También puede ser beneficioso el **reemplazo hormonal con estrógenos o de estrógenos más progesterona**, así como el **uso de antidepresivos como la desvenlafaxina** a una dosis de 100 mg, la cual ayuda a disminuir los síntomas vasomotores asociados al proceso de transición.

Received: 23 August 2019 | Accepted: 14 September 2019

DOI: 10.1002/brb3.1441

ORIGINAL RESEARCH

Brain and Behavior Open Access WILEY

# Trend of antidepressants before, during, and after pregnancy across two decades—A population-based study

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**Funding information**
Independent Research Fund Denmark, Grant/Award Number: 9039-00296B; Novo Nordisk Foundation, Grant/Award Number: NNF16OC0019126; Fabrikant Vilhelm Pedersen og Hustrus Legat; National Institute of Mental Health (NIMH), Grant/Award Number: R01MH104468; Danish Epilepsy Association; AUFF NOVA, Grant/Award Number: AUFF-E 2016-9-25; Central Denmark Region; iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Grant/Award Number: R155-2014-1724; Danish Council for Independent Research, Grant/Award Number: DFF-5053-00156B; Lundbeck Foundation for Travel Stipends, Grant/Award Number: R315-2019-659

## Abstract

**Introduction:** Factors that influence antidepressant (AD) prescription and use during pregnancy are multiple including, in particular, the balance between the potential risk of untreated depression and the potential risk of AD treatment. Surveillance of temporal trends of AD use might identify areas requiring further research. We studied the use of ADs before, during, and after pregnancy using national data across two decades in Denmark.

**Methods:** We included 1,232,233 pregnancies leading to live birth in Denmark between 1 January 1997 and 31 December 2016. Information on redemption of AD prescriptions was obtained from the Danish National Prescription Register.

**Results:** We identified 29,504 (2.4%) pregnancies having at least one AD prescription (96,232 AD prescriptions) during pregnancy. The majority redeemed more than one prescription (69.7%) often for a single kind of AD (83.5%), and in 94% of the AD-exposed pregnancies, the estimated duration of treatment was 1 month or longer. Prescription of ADs during pregnancy increased steadily from 0.4% in 1997 to 4.6% in 2011, but decreased thereafter to 3.1% in 2016. The proportion of pregnancies with ADs in 2011 was 6.05-fold higher than that in 1997. The temporal trends in AD prescription in the years before and after pregnancy were similar to the trend during pregnancy. The decreasing use of ADs during pregnancy after 2011 was mainly driven by a decrease in the use of selective serotonin reuptake inhibitors (SSRIs), especially citalopram, the main type of SSRIs used in Denmark.

**Conclusion:** Prescription of ADs during pregnancy in Denmark increased steadily from 1997 to 2011 but decreased sharply thereafter. More research is needed to show whether the same trend exists in other populations, like women of reproductive age, men of reproductive age, and old people, and other countries. We also need to find explanation for the decreasing trend in recent years and potential risk for untreated depression.

KEYWORDS
antidepressants, depression, epidemiology, pregnancy

## SIGNIFICANT OUTCOMES

The proportion of pregnant women who redeemed antidepressants (ADs) during pregnancy increased six-fold from 1997 to 2011, but decreased sharply thereafter—similar trends were found before and after pregnancy.

The decrease in the use of ADs after 2011 was mainly driven by a decrease in the prescribing of serotonin reuptake inhibitors (SSRIs) and in particular citalopram, the main type of SSRI used in Denmark.

## LIMITATIONS

Redeeming prescribed ADs during pregnancy is not always equivalent to the use of ADs, and exposure during pregnancy may thus be lower than estimated from pharmacy data.

## 1 | INTRODUCTION

The prevalence of depression during pregnancy is substantial (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Gavin et al., 2005), and use of antidepressants (ADs) during pregnancy has increased in most developed countries in recent decades (Andrade et al., 2008; Jimenez-Solem et al., 2013; Molenaar, Lambregtse-van den Berg, & Bonsel, 2019). Antidepressant drug use during pregnancy increased from 2.0% of deliveries in 1996 to 7.6% of deliveries in 2004 and 2005 in the United States (Andrade et al., 2008). Dispensing rates of selective serotonin reuptake inhibitors (SSRIs) steadily increased in Netherland from 0.8% in 1999/2000 to 2.1% in 2013/2014 (Molenaar et al., 2019). In Denmark, the rate of AD exposure during pregnancy increased from 0.2% in 1997 to 3.2% in 2010 (Jimenez-Solem et al., 2013).

Factors that influence AD use during pregnancy are multiple and include social, cultural, and economic factors, but in particular, the balance between the potential risk of AD treatment and untreated depression to fetus and pregnant women (Gentile, 2017; Gomez-Lumbreras et al., 2019; Grigoriadis et al., 2013; Petersen, Gilbert, Evans, Man, & Nazareth, 2011; Prady, Hanlon, Fraser, & Mikocka-Walus, 2018). Concerns about the safety of AD exposure to unborn babies are a major determinant of cessation of AD medication use during pregnancy (Petersen et al., 2011), although pregnancy can represent a time of increased vulnerability for the onset or return of depression (Bennett et al., 2004). The postpartum period is also a vulnerable time period with concerns of safety of medicine via breastfeeding and increasing demand for prescriptions of ADs (Munk-Olsen, Gasse, & Laursen, 2012). Most studies have indicated that new types of ADs-like selective serotonin reuptake inhibitors (SSRIs) are generally safe and not associated with birth defects or neurodevelopmental impairment (Petersen, Evans, Gilbert, Marston, & Nazareth, 2016; Prady et al., 2018), which might partly explain the increasing use of AD (and SSRIs in particular) during pregnancy in most countries. Side effects of AD use to the pregnant women are also important factors, which might affect prescriptions of ADs from physicians and adherence of AD use. Surveillance of temporal trends in AD use is basic and essential to research on health of pregnant women and unborn babies and might inform potential safety signals and identify areas requiring further research (Charlton et al., 2015).

In this study, we present the use of ADs in Denmark before, during, and after pregnancy between 1997 and 2016.

## 2 | MATERIAL AND METHODS

### 2.1 | Study population

We identified pregnancies leading to live birth between 1 January 1997 and 31 December 2016 in Denmark ($N$ = 1,243,729) from the Danish Medical Birth Registry (Bliddal, Broe, Pottegard, Olsen, & Langhoff-Roos, 2018; Knudsen & Olsen, 1998). We excluded pregnancies where the pregnant woman's identification number was missing ($n$ = 9), pregnancies that had a missing value of gestational age ($n$ = 11,363) or gestational age <20 weeks ($n$ = 124), leaving 1,232,233 pregnancies in the study population. In Denmark, all residents are assigned a unique identification number recorded in the Danish Civil Registration System (Schmidt, Pedersen, & Sorensen, 2014), and this identification number enables linkage between the many nation-wide registries, such as the Danish Medical Birth Registry and the Danish National Prescription Registry (Kildemoes, Sorensen, & Hallas, 2011) we used in this study. The study was a population-based study and approved by the Danish Data Protection Agency.

### 2.2 | Information on redeeming of ADs

Information on redeemed AD prescriptions was obtained from the Danish National Prescription Registry (Kildemoes et al., 2011), which contains data on all prescription medications dispensed from Danish community pharmacies since 1995. The registry has applied codes for medications using the anatomical therapeutic chemical (ATC) system. ADs were identified by the ATC code N06A. ADs were further categorized into the following groups: selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic ADs (TCAs), and other ADs (ATC codes are found in Table S1). The register contains information on number of package of a medicine in a prescription and the number of defined daily dose (DDD) in one package. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO, 2018).

### 2.3 | Information on pregnancy

Information on gestational age and the age of pregnant women at the time of birth was obtained from the Danish Medical Birth Registry (Knudsen & Olsen, 1998). Information on gestational age was reported in days by the midwife attending the delivery using a mandatory coding sheet. Ultrasound measurements have been

**TABLE 1** Antidepressant (AD) prescriptions redeemed during pregnancy in Denmark between 1997 and 2016

| Profiles | *N* = 29,504 No. | % |
|---|---|---|
| Number of AD prescription per pregnancy | | |
| 1 | 8,925 | 30.3 |
| 2 | 5,641 | 19.1 |
| 3 | 5,111 | 17.3 |
| 4 | 2,993 | 10.1 |
| 5 | 2,064 | 7.0 |
| 6 | 1,630 | 5.5 |
| 7+ | 3,140 | 10.6 |
| Number of kind of AD per pregnancy | | |
| 1 | 24,643 | 83.5 |
| 2 | 4,315 | 14.6 |
| 3+ | 546 | 1.9 |
| Type of and specific AD prescribed during pregnancy | | |
| Tricyclic AD (nonselective monoamine reuptake inhibitors) | 1,895 | 6.4 |
| Selective serotonin reuptake inhibitors (SSRIs) | 24,173 | 81.9 |
| Zimeldine | 0 | 0 |
| Fluoxetine | 5,117 | 17.3 |
| Citalopram | 10,168 | 34.5 |
| Paroxetine | 1,766 | 6.0 |
| Sertraline | 7,967 | 27 |
| Alaproclate | 0 | 0 |
| Fluvoxamine | 23 | 0.1 |
| Etoperidone | 0 | 0 |
| Escitalopram | 1,892 | 6.4 |
| Serotonin–norepinephrine reuptake inhibitors (SNRIs) | 3,857 | 13.1 |
| Venlafaxine | 3,230 | 10.9 |
| Milnacipran | 0 | 0 |
| Duloxetine | 679 | 2.3 |
| Desvenlafaxine | 0 | 0 |
| Others | 2,115 | 7.2 |
| Nonselective monoamine oxidase inhibitors | NA | NA |
| Monoamine oxidase A inhibitors | 13 | 0 |
| Norepinephrine–dopamine reuptake inhibitors (NDRIs) | 197 | 0.7 |

*Note:* NA: The number is <4 and not available according to data protection guidelines from Denmark Statistics.

**TABLE 2** Duration AD prescriptions during pregnancy might cover according to defined daily dose (DDD) of a drug for maintenance for its main indication

| Duration AD prescriptions during pregnancy might cover | No. | % |
|---|---|---|
| All prescriptions (*N* = 96,232) | | |
| <1 month | 11,054 | 11.5 |
| 1 month | 28,998 | 30.1 |
| 2 months | 13,391 | 13.9 |
| 3 months | 28,111 | 39.2 |
| 4–7 months | 13,922 | 14.5 |
| 8+ months | 756 | 0.8 |
| All pregnancies with one kind of AD during pregnancy (*N* = 24,643) | | |
| <1 month | 1,478 | 6.0 |
| 1 month | 3,483 | 14.1 |
| 2 months | 2,105 | 8.5 |
| 3 months | 3,476 | 14.1 |
| 4–7 months | 4,591 | 18.6 |
| 8+ months | 9,510 | 38.6 |
| Pregnancies with one prescription of same AD | | |
| <1 month | 1,367 | 15.3 |
| 1 month | 3,032 | 34.0 |
| 2 months | 942 | 10.6 |
| 3 months | 2,667 | 29.9 |
| 4–7 months | 828 | 9.3 |
| 8+ months | 89 | 1.0 |
| Pregnancies with two prescriptions of same AD | | |
| <1 month | 106 | 2.1 |
| 1 month | 356 | 7.2 |
| 2 months | 984 | 19.9 |
| 3 months | 347 | 7.0 |
| 4–7 months | 2,159 | 43.8 |
| 8+ months | 982 | 19.9 |
| Pregnancies with three prescriptions of same AD | | |
| <2 months | 77 | 1.8 |
| 2 months | 111 | 2.5 |
| 3 months | 378 | 8.7 |
| 4–7 months | 685 | 15.7 |
| 8+ months | 3,115 | 71.3 |
| Pregnancies with four and more prescriptions of same AD | | |
| <2 months | 23 | 0.3 |
| 2 months | 68 | 1.1 |
| 3 months | 84 | 1.3 |
| 4–7 months | 919 | 14.3 |
| 8+ months | 5,324 | 83.0 |

*Note:* One month is 28 days.

widely used to determine gestational age in nearly all pregnancies since 1995 (Jorgensen, 1999). Gestational age was used to estimate the time of conception by subtracting gestational age from the birth date. Information on diagnosis of depression and other psychiatric disorders before the time of delivery was obtained from the Danish Psychiatric Central Register, in which the International Classification of Diseases (ICD), 8th revision was used between

1966 and 1993 and 10th revision was used from 1994 onwards (Mors, Perto, & Mortensen, 2011; Munk-Jorgensen & Mortensen, 1997). The codes we used to identify depression and other psychiatric disorders are shown in Table S2. To identify ADs that were prescribed before conception but may have been consumed by women in the early period of pregnancy, we defined the study period of pregnancy as the period from 1 month (30 days) before the estimated time of conception until birth. We also defined the two periods around pregnancy as 1 year (365 days) before and after pregnancy (1 year before pregnancy was defined as the period between 395 and 30 days before the conception). We used the common concept on periods of 1 year before and after pregnancy since we aimed to present temporal trend before and after pregnancy as well rather than comparing the exact prevalence of AD in the three periods.

## 2.4 | Statistical analyses

For pregnancies with at least one AD prescription, we analyzed the number of AD prescription per pregnancy, the number of kind of AD per pregnancy, proportion of pregnancies with a type of AD (SSRIs, SNRIs, TCAs) or each specific AD, and the estimated duration that AD prescriptions during pregnancy might cover. If two or more kinds of ADs were prescribed on the same day, the prescription for each kind of AD was counted as a single prescription. We presented AD prescriptions with two kinds of ADs redeemed during pregnancy, which could be treatment with two kinds of AD or change from one kind of AD to another. We calculated the estimated duration that an AD prescription might cover by multiplying the number of redeemed packs with the number of defined daily doses (DDD) in one package. The total duration that AD prescriptions during pregnancy might cover was the summary of duration of all prescriptions during pregnancy. We presented duration for individual prescriptions and duration that all AD prescriptions might cover for pregnancies with one kind of AD during pregnancy. We presented proportion of pregnancies where women delivered at three age groups (<25, 25–34, 35+ years old) and proportion of pregnancies with a history of psychiatric disorders before the time of delivery (depression, other psychiatric disorders, or no psychiatric disorder) since the two factors could affect prescription and use of ADs.

We analyzed the temporal trend of overall AD prescriptions, and trends according to types of ADs, and specific AD during pregnancy. We analyzed the temporal trend of AD prescriptions in the 1 year before and 1 year after pregnancy. We further analyzed the trends in overall AD prescriptions according to pregnant women's age at the time of birth and the pregnant women's history of psychiatric disorders before the time of delivery dating back to 1969 (Mors et al., 2011). We analyzed the temporal trend of AD prescriptions during pregnancy by adjusting for the pregnant women's age at time of birth and the history of psychiatric disorders before the birth using a generalized linear model. We specified that the distribution of AD prescriptions is a Poisson distribution, the link function is logarithm,

**TABLE 3** Antidepressant (AD) prescriptions with two types of AD during pregnancy ($N$ = 4,315)[a]

| AD | Tricyclic AD | | Fluoxetine | | Citalopram | | Paroxetine | | Sertraline | | Escitalopram | | SNRIs | | Other ADs | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Tricyclic AD | | | 49 | 1.1 | 89 | 2.1 | 21 | 0.5 | 103 | 2.4 | 18 | 0.4 | 62 | 1.4 | 34 | 0.8 | 451 | 10.5 |
| Fluoxetine | 49 | 1.1 | | | 464 | 10.8 | 201 | 4.7 | 474 | 11.0 | 108 | 2.5 | 240 | 5.6 | 120 | 2.8 | 1,657 | 38.4 |
| Citalopram | 89 | 2.1 | 464 | 10.8 | | | 93 | 2.2 | 370 | 8.6 | 283 | 6.6 | 217 | 5.0 | 223 | 5.2 | 1,739 | 40.3 |
| Paroxetine | 21 | 0.5 | 201 | 4.7 | 93 | 2.2 | | | 87 | 2.0 | 7 | 0.2 | 9 | 0.2 | 22 | 0.5 | 440 | 10.2 |
| Sertraline | 103 | 2.4 | 474 | 11.0 | 370 | 8.6 | 87 | 2.0 | | | 130 | 3.0 | 363 | 8.4 | 213 | 4.9 | 1,742 | 40.4 |
| Escitalopram | 18 | 0.4 | 108 | 2.5 | 283 | 6.6 | 7 | 0.2 | 130 | 3.0 | | | 38 | 0.9 | 39 | 0.9 | 623 | 14.4 |
| SNRIs | 62 | 1.4 | 240 | 5.6 | 217 | 5.0 | 9 | 0.2 | 363 | 8.4 | 38 | 0.9 | | | 116 | 2.7 | 1,078 | 25.0 |
| Other ADs | 34 | 0.8 | 120 | 2.8 | 223 | 5.2 | 22 | 0.5 | 213 | 4.9 | 39 | 0.9 | 116 | 2.7 | | | 778 | 18 |
| Total | 451 | 10.5 | 1,657 | 38.4 | 1,739 | 40.3 | 440 | 10.2 | 1,742 | 40.4 | 623 | 14.4 | 1,078 | 25.0 | 778 | 18 | | |

Abbreviations: SNRIs, Serotonin–norepinephrine reuptake inhibitors; SSRIs, Selective serotonin reuptake inhibitors refer to fluoxetine, citalopram, paroxetine, sertraline, escitalopram in the table.
[a]The two types of AD could be a multitherapy of AD treatment or a change of AD from one type to another. Four pregnancies with a prescription of fluvoxamine during pregnancy were not included in the table because the numbers were too small according to data protection guidelines from Denmark Statistics.

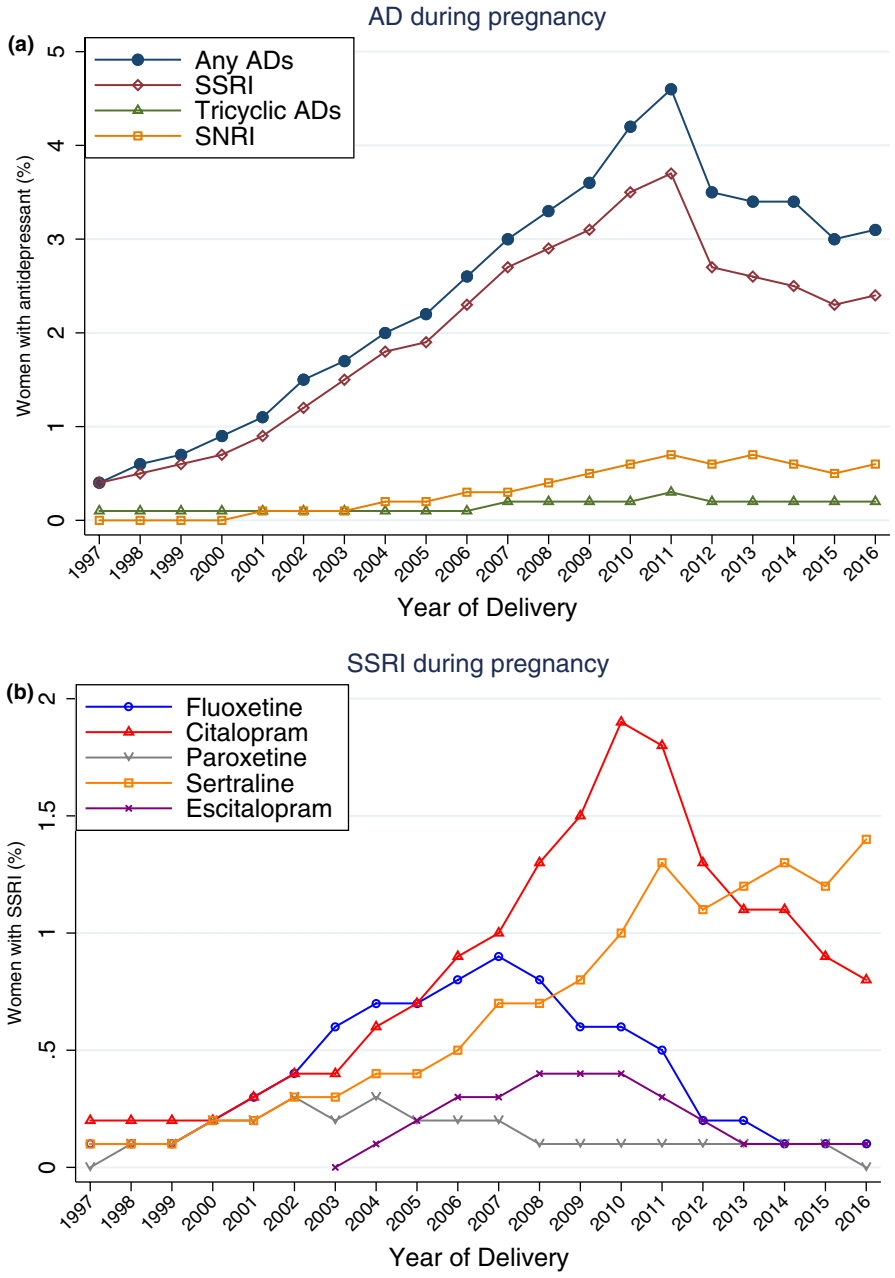


**FIGURE 1** Trends in antidepressant prescriptions including types (upper panel) of and specific AD (bottom panel) during pregnancy in women who gave birth between 1997 and 2016 in Denmark

and women from different pregnancies are a cluster factor. The unit in the analyses was pregnancy, and one woman could have several pregnancies.

The analyses were conducted in STATA 15.1 (StataCorp LLC).

## 3 | RESULTS

In the whole cohort, we identified 29,504 (2.4%) pregnancies where the pregnant women redeemed at least one AD prescription from 30 days before pregnancy to the date of the birth.

Among the 29,504 pregnancies where the pregnant women redeemed prescriptions for ADs during pregnancy, 30.3% redeemed one AD prescription and 69.7% redeemed two or more AD prescriptions including 50.6% with three or more AD prescriptions (Table 1).

We identified 96,232 AD prescriptions in total during all pregnancies. Of all the pregnancies with AD prescriptions during pregnancy, 24,643 (83.5%) pregnant women had redeemed only one kind of AD, while 4,315 (14.6%) redeemed two kinds of ADs, and 546 (1.9%) redeemed three or more kinds of ADs. In total, 81.9% of pregnancies were exposed to SSRIs, 13.1% to SNRIs, and 6.4% to TCAs. Citalopram, sertraline, and fluoxetine were the main types of SSRIs prescribed during pregnancy (Table 1).

Most AD prescriptions (88.5%) cover treatment for 1 month or longer. In 94% of the AD-exposed pregnancies, the estimated duration of treatment was 1 month or longer (Table 2). Even among pregnancies with only one AD prescription, 84.7% would cover 1 month or longer (Table 2).

Among 4,315 pregnancies with two types of ADs during pregnancy, the most common combinations were fluoxetine and

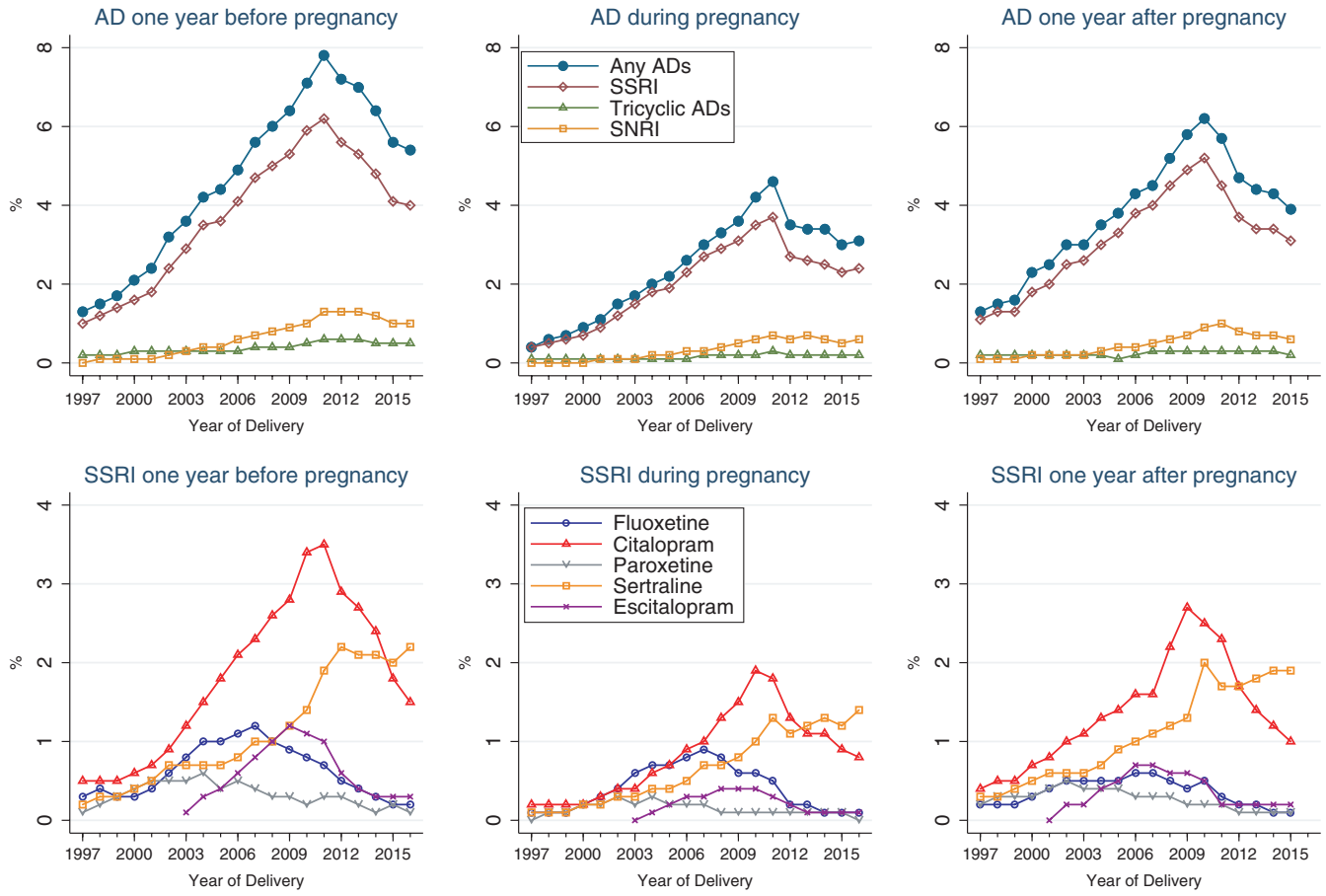


**FIGURE 2** Trends in antidepressant prescriptions including types (upper panel) of and specific AD (bottom panels) before, during, and after pregnancy in women who gave birth between 1997 and 2016 in Denmark

sertraline (11.0%), fluoxetine and citalopram (10.8%), citalopram and sertraline (8.6%), and sertraline and SNRIs (8.4%) (Table 3).

The proportion of pregnant women who gave a birth at 35 years old and above was 12.7% in 1997 and 20.7% in 2016 (Table S3). The mean age of pregnant women at time of birth was 29.1 (standard deviation [*SD*]: 4.7) in 1997 and 30.3 (*SD*: 5.0) in 2016. The proportion of pregnant women who were diagnosed with depression and other psychiatric disorders before birth increased from 1997 to 2016 (Table S4).

The proportion of pregnancies with AD prescriptions rose steadily from 0.4% in 1997 to 4.6% in 2011, but decreased thereafter to 3.1% in 2016 (Figure 1). The decreasing use of ADs during pregnancy after 2011 was mainly driven by a decrease in use of SSRIs. Prescriptions of SNRIs also peaked in 2011 and slightly levelled off afterward. Among the individual SSRIs, prescription of citalopram and escitalopram decreased, and prescription of sertraline levelled off from 2011, while prescription of fluoxetine began to decrease from 2008 (Figure 1). Temporal trends in the prescription of ADs before and after pregnancy were similar to the pattern of AD prescription during pregnancy (Figures S1 and S2). The proportion of women who redeemed prescriptions for ADs in the year before pregnancy was 1.3%, 7.8%, and 5.4% for those delivered in 1997, 2011, and 2016, respectively. The proportion of women who redeemed prescriptions for ADs in the year after pregnancy was 1.3%, 5.7%, and 3.9% for those delivered in 1997, 2011, and 2015, respectively. The temporal trends of AD prescriptions before, during, and after pregnancy are shown in Figure 2. Information about AD prescriptions in the year after pregnancy among pregnancies delivered in 2016 is not shown in the figure since most of the women who gave birth in 2016 were not completely followed for 1 year since the prescription data were only available till the year 2016.

Figure 3 shows the temporal trend in AD prescriptions during pregnancy according to the age at time of delivery and the history of psychiatric disorders of pregnant women. Redemption of AD prescriptions among women <25 years of age increased faster than among the other two groups of pregnant women (25–34 years of age and 35+ years of age), but all had a decrease in the use of ADs after 2011 (Figure 3). Temporal trends in AD prescriptions among pregnant women with and without a history of psychiatric disorders were different among the three groups, but all had a decrease in the use of ADs after 2011 (Figure 3). Temporal trends in the prescription of ADs in 1 year before and 1 year after pregnancy according to the age of the pregnant women and the history of psychiatric disorders before birth are shown in Figures S3 and S4. The temporal trends in antidepressant prescriptions

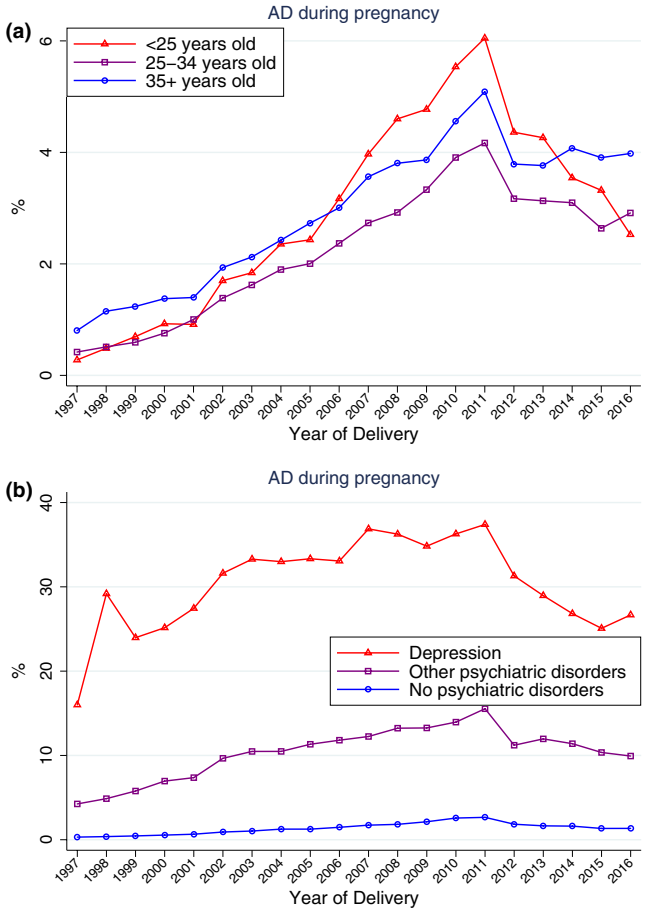


**FIGURE 3** Trends in antidepressant prescriptions during pregnancy among women who gave birth in Denmark between 1997 and 2016 according to the age of the pregnant women (upper panel) and the history of psychiatric disorders before birth (bottom panel)

before, during, and after pregnancy according to the age of the pregnant women and the history of psychiatric disorders before birth are shown in Figure 4. After adjusting for the age of women at the time of birth and the history of psychiatric disorders before birth, the proportion of prescriptions of ADs during pregnancy in 2011 was 6.05-fold (95% CI: 5.37–6.82) higher compared with the proportions in 1997 (Figure 5).

## 4 | DISCUSSION

Our study showed that 2.4% of all included pregnancies in Denmark during 1997 and 2016 had at least one AD prescription during pregnancy. In pregnancies with ADs, the majority redeemed more than one prescription (69.7%), most often for a single kind of AD (83.5%). Furthermore, in 94% of the AD-exposed pregnancies, the estimated duration of treatment was 1 month or longer. SSRIs dominated in Denmark, and citalopram was the main type of SSRIs used in Denmark. The more impressive findings were that the proportion of pregnancies with AD prescriptions during pregnancy increased steadily from 1997 to 2011, but decreased sharply thereafter to the end of the study period in 2016. The decreasing trend in AD prescriptions in recent years was also found before and after pregnancy. The decrease in redeeming of AD prescriptions was driven mainly by a decrease in prescription of citalopram.

This was a population-based study covering the entire population of pregnancies in Denmark over 20 years. Both the estimation of the duration of pregnancy (gestational age) and information on ADs were captured from nation-wide registries, and these data are therefore not subject to recall bias. The quality of prescription data is also generally held to be high because of the Danish pharmacy reimbursement structure according to which all citizens receive reimbursement from the Danish regions. Reimbursement is automatically deducted from the price charged at the pharmacy. However, redeeming ADs is not always equivalent to using ADs. A study on the data quality of prescription registration in Denmark indicates that completeness of psychoanaleptics (N06) is 95.1% (Johannesdottir et al., 2012). A study in Denmark has shown that about 85% of people who were prescribed ADs took them regularly, which may also apply to AD use before women were aware of their pregnancy (Lewer, O'Reilly, Mojtabai, & Evans-Lacko, 2015). A large proportion of pregnancies (50.6%) in our study had three or more AD prescriptions, and they were more likely to continue use AD during pregnancy.

The types of ADs used in pregnancy vary across countries (Abbing-Karahagopian et al., 2014; Zoega et al., 2015). Since the 90s, use of SSRIs in Europe has increased while use of TCAs has remained stable or decreased except in Germany (Abbing-Karahagopian et al., 2014). However, type of SSRIs varies across countries even among the homogeneous Scandinavian countries where citalopram was more often prescribed for pregnant women in Denmark, while sertraline dominated in Iceland and escitalopram dominated in Norway (Zoega et al., 2015). In pregnancies where the women filled two or more kinds of ADs during pregnancy, we did not separate the different situations like combination therapy with two or more kinds of ADs at the same time or change of AD from one kind to another (Benard-Laribiere et al., 2018). This could be a group of interest for further studies.

Studies have shown that many factors including pharmaceutical expenditure, clinical factors, indications for use and patient, and doctor characteristics, can affect the prescription and use of Ads (Bauer et al., 2008; Gomez-Lumbreras et al., 2019). In August 2011, the US Food and Drug Administration issued a safety warning concerning the safety of high doses of citalopram, as the administration of high doses was associated with cardiac corrected QT interval (QTc) prolongation according to findings from an unpublished randomized controlled trial (Howland, 2011). Citalopram was the most often prescribed AD to Danish pregnant women in 2011. This safety concern could, therefore, be one of the main explanations for the decreasing trend in AD use in Danish pregnant women after 2011, although the most recent guidelines published in 2010 for general practitioners in Denmark recommended that perinatal mental disorders should be pharmacologically treated (Munk-Olsen et al., 2012;

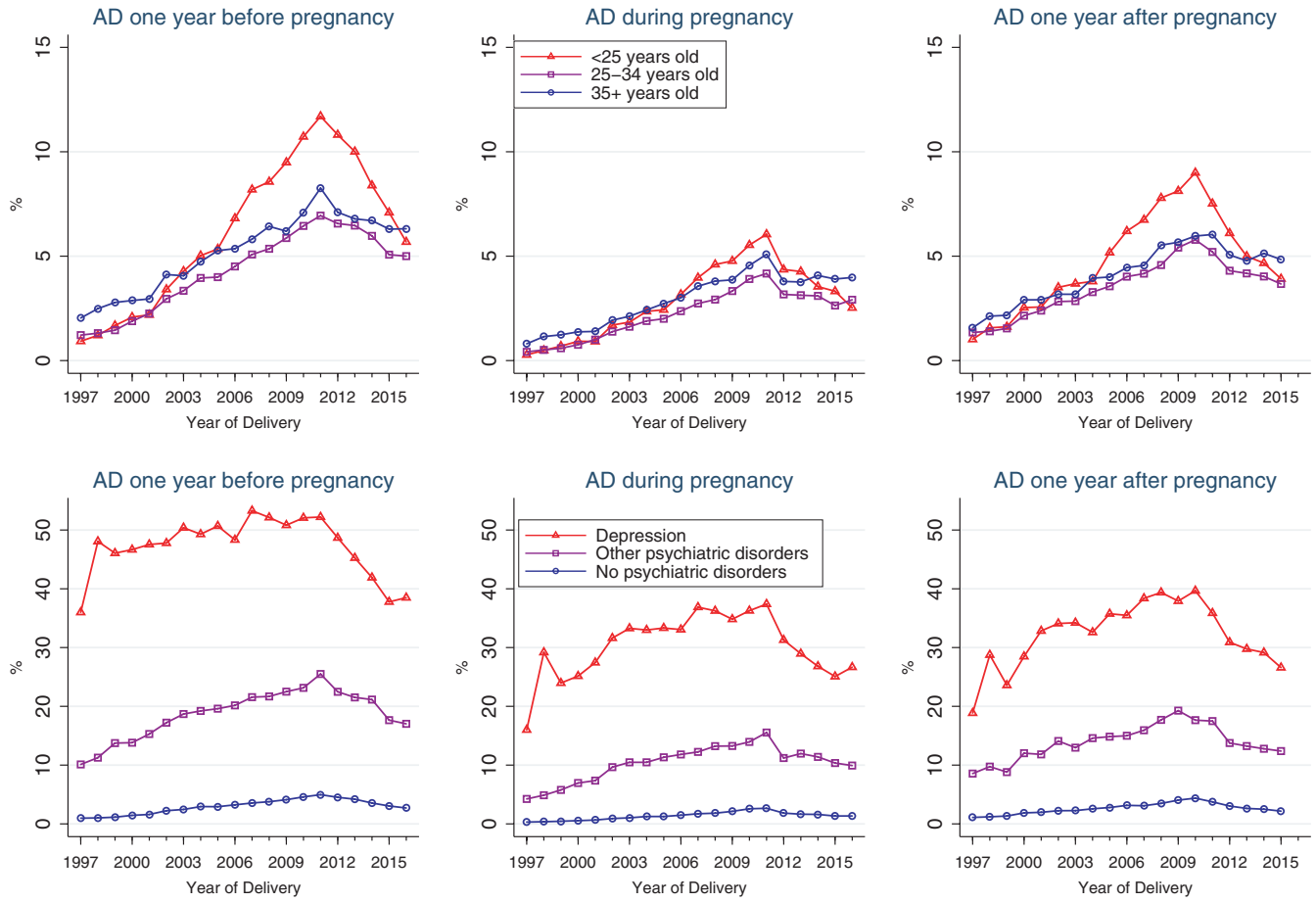


**FIGURE 4** Trends in antidepressant prescriptions before, during, and after pregnancy among women who gave birth in Denmark between 1997 and 2016 according to the age of the pregnant women (upper panels) and the history of psychiatric disorders before birth (bottom panels)

Zoega et al., 2015). It is still unknown whether the decreasing trend after 2011 is related to suboptimal treatment women with depression. Further studies are needed to determine time trends in other countries and especially whether the trends in AD prescriptions (e.g., of citalopram) show similar trends to those observed in this study.

In general, there was an increase in the proportion of prescriptions of ADs with increasing age of the pregnant woman (Abbing-Karahagopian et al., 2014). Maternal age at birth increased slightly during the study period. The proportion of pregnant women who were diagnosed with depression or other psychiatric disorders before birth increased also with time, but both the age and history of depression or other psychiatric disorders could not explain the temporal trend of AD since the trend remained after adjustment for these factors.

Our study showed that the proportion of women (same as pregnancies) who redeemed AD prescriptions during pregnancy was lower than the proportion of women who redeemed AD prescriptions in the year before pregnancy and the year after pregnancy. We should be aware that the pregnancy period, which is usually around 9 or 10 months in this study since we included 1 month before pregnancy, is shorter than the other two periods, which are 1 year before and after pregnancy. It may slightly affect the proportion of women with AD prescription in these periods although it was unlikely to change the trend over time. Although the study population in the year before pregnancy comprised women who were not pregnant, they may not be representative of the general population of women of fertile age because pregnant women or women who are planning a pregnancy may overall be healthier than women of the same age who are not pregnant. Further studies are needed to determine whether the trend in AD prescriptions in the population of women of fertile age, men of fertile age, or old people follows the same pattern as that seen around pregnancy among pregnant women.

This study showed that the prevalence of AD use in 1 year after birth was higher than AD use during pregnancy, but lower than AD use in 1 year before pregnancy. The time after birth is a vulnerable time for new mothers and may herald the potential onset of new psychiatric conditions such as postpartum depression (Munk-Olsen et al., 2016). At the same time, women are still cautious of taking medicine at the postpartum period especially when they are breastfeeding. A previous study showed that it takes about 2 years after birth to reach the prevalence level of AD use before pregnancy (Jimenez-Solem et al., 2013).

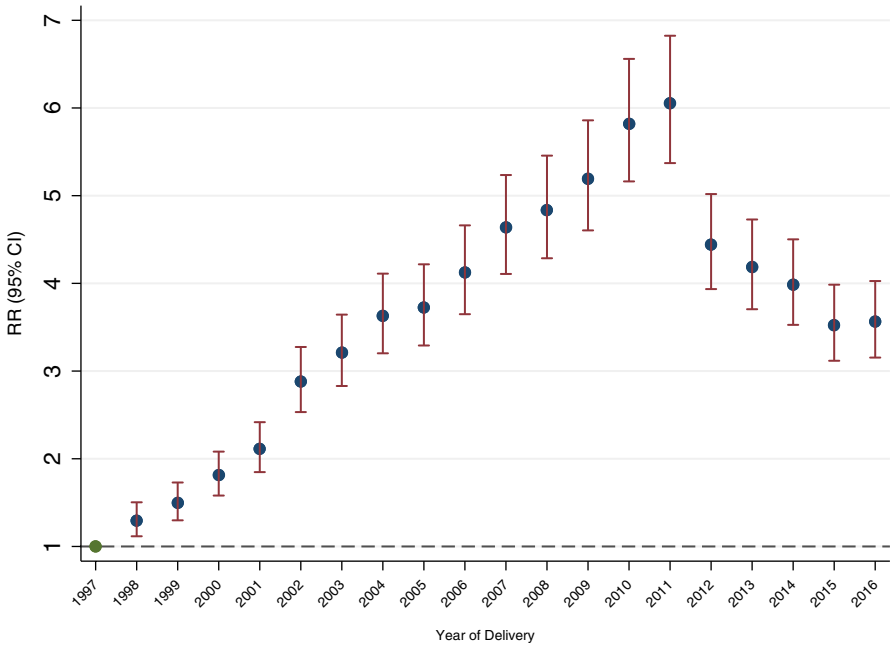


**FIGURE 5** The risk ratio (RR) of redemption of AD prescriptions during pregnancy between 1998 and 2016 in Denmark compared with the prescription in 1997

In UK and Wales, however, prescription of SSRI after birth was higher than prescription of SSRI before pregnancy (Charlton et al., 2015).

In conclusion, AD prescription before, during, and after pregnancy in Denmark rose steadily from 1997 and peaked in 2011 but has decreased sharply in recent years. The decrease in the trend of AD prescriptions was explained mainly by citalopram, the main type of SSRIs used in Denmark. More research is needed to show whether the same trend exists in other population, like women of reproductive age, men of reproductive age, and old people, and in other countries. More research is needed to find the explanation for the decreasing trend in recent years and the influence of the increasing and decreasing use of ADs during pregnancy for the health of pregnant women and their offspring.

## ACKNOWLEDGMENTS

The study was supported by the Danish Epilepsy Association, Central Denmark Region, and the Novo Nordisk Foundation (NNF16OC0019126). Y. Sun is supported by the Independent Research Fund Denmark (9039-00296B) and Lundbeck Foundation for Travel Stipends (R315-2019-659). Liu X. is supported by the Danish Council for Independent Research (Project No. DFF-5053-00156B). K.G. Ingstrup and M.M Lund are supported by AUFF NOVA, grant number: (AUFF-E 2016-9-25). Munk-Olsen T. is supported by iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724), The National Institute of Mental Health (NIMH) (R01MH104468) and Fabrikant Vilhelm Pedersen og Hustrus Legat.

## CONFLICT OF INTEREST

Dr. Christensen reported receiving honoraria from serving on the scientific advisory boards of, and giving lectures for, UCB Nordic and Eisai AB, as well as receiving travel funding from UCB Nordic. No other disclosures were reported.

## AUTHOR CONTRIBUTIONS

Dr. Sun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sun, Dreier, Christensen, Liu, Ingstrup, Mægbæk, and Munk-Olsen are involved in concept and design. Sun, Dreier, Christensen, Liu, Ingstrup, Mægbæk, and Munk-Olsen are involved in acquisition, analysis, and interpretation of data. Sun drafted the manuscript, and Sun, Dreier, Christensen, Liu, Ingstrup, Mægbæk, and Munk-Olsen performed critical revision of the manuscript for important intellectual content. Sun and Dreier statistically analyzed; Christensen obtained funding; and Christensen supervised.

## DATA AVAILABILITY STATEMENT

Data from the national prescription and medical birth registers used in this study are available and owned by the national health register holders in Denmark that provided permissions. Researchers can obtain access to individual-level anonymized data via servers at Statistics Denmark and the Danish Health Data Authority.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Sun Y, Dreier JW, Liu X, et al. Trend of antidepressants before, during, and after pregnancy across two decades—A population-based study. *Brain Behav*. 2019;9:e01441. https://doi.org/10.1002/brb3.1441

Archives of Women's Mental Health (2020) 23:71–79
https://doi.org/10.1007/s00737-019-0951-5

ORIGINAL ARTICLE

# Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands

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Received: 13 August 2018 / Accepted: 31 January 2019 / Published online: 14 February 2019


## Abstract

Management of mental illness in the perinatal period with antidepressants is controversial, since evidence emerged on potential harmful effects to the unborn child. However, over time, the dispensing of antidepressants in the perinatal period has increased. We examined perinatal dispensing patterns over time and the role of a recently issued guideline in this regard. We identified a 16-year cohort of 153,952 Dutch pregnancies with a delivery date between January 1999 and December 2014. Data included exposure to selective serotonin reuptake inhibitors (SSRIs) related to phases of pregnancy (preconception, pregnancy and delivery, post-delivery). The chi-square test for trends was used. With standard logistic regression, we explored the influence of patient characteristics on continuation of SSRIs during pregnancy. A persistent significant rise of dispensing rates in all phases was observed, with the largest increase during pregnancy (from 0.8% in 1999/2000 to 2.1% in 2013/2014, chi-square for trend = 141.735, $p < 0.001$). A substantial change of practice in terms of the SSRI used (less paroxetine) and the policy towards continuation into pregnancy (more continuation over time) was visible. Concomitant use of psycholeptics halved the probability of continuation of SSRIs (OR 0.50, 95%CI 0.43–0.55, $p < 0.01$). Dispensing rates of SSRIs steadily increased last 16 years, especially during pregnancy, caused by an increase in the proportion of women continuing their medication during pregnancy. In view of the demonstrated impact of uncertainty regarding effectiveness and safety of SSRIs in pregnancy, future research should involve more detailed outcome research of SSRIs as it is, and research into viable alternatives.

**Keywords** Antidepressants · Pregnancy · Dispensing · Serotonin · Pharmacoepidemiology

## Introduction

Management of mental illness in the perinatal period[1] is an ongoing topic of professional and public debate. Administration of psychotropic medication is a common treatment option (McAllister-Williams et al. 2017), with antidepressants most frequently prescribed (Daw et al. 2012), especially selective serotonin reuptake inhibitors (SSRIs) (Cooper et al. 2007). Over the years, the prescription of perinatal SSRIs increased (Bakker et al. 2008; Charlton et al. 2015; Cooper et al. 2007; Jimenez-Solem et al. 2013), leading to prescription rates of 1.7 to 10.2% during pregnancy (Charlton et al. 2015; Cooper et al. 2007; Hurault-Delarue et al. 2018).

[1] In this study defined as the entire period of pregnancy, the preconception period and the postnatal period (first year after birth).

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00737-019-0951-5) contains supplementary material, which is available to authorized users.

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Perinatal SSRI use has become controversial as evidence emerged on potential harmful effects to the unborn child (Simoncelli et al. 2010). Its use has been reported to increased risks for cardiovascular malformations (especially paroxetine) (Grigoriadis et al. 2013b), persistent pulmonary hypertension of the neonate (Kieler et al. 2012), poor neonatal adaptation (Grigoriadis et al. 2013a), preterm delivery, lower birth weight (Ross et al. 2013) and psychiatric disorders in later life (Liu et al. 2017). Untreated depression during pregnancy, however, also bears risk for the child: associations with premature delivery, low birth weight and perinatal mortality have been reported (Grigoriadis et al. 2013c; Grote et al. 2010; Howard et al. 2007). In early childhood, it can lead to behavioural, emotional, cognitive and motor problems (Field 2011; Talge et al. 2007).

Any affected pregnant woman, and their health care professional, therefore faces a complex decision regarding initiation, continuation or discontinuation of SSRIs. Internationally, guidelines agree on a limited set of recommendations, such as the use of psychotherapy as preferred treatment in mild to moderate depression (Molenaar et al. 2018b). But on key aspects of the dilemma, guidelines are unclear (conflicting recommendations or no reference to the topic), i.e., on the first-choice drug and on when and how to switch to another antidepressant, leading to considerable variation in current practice (Molenaar et al. 2018a; Ververs et al. 2009).

In this study, we present population-based information on SSRI dispensing and dispensing patterns related to the pregnancy phases covering 16 years in the Netherlands. We focus on specific SSRIs, expecting a paroxetine decline at the time emerging evidence suggested excess risks of paroxetine on child outcome. Furthermore, we explore the effect of the introduction of the Dutch multidisciplinary guideline in 2012 (NVOG 2012) on continuation of SSRI use during pregnancy. The guideline recommends continuing SSRIs (without switching) in the perinatal period if women are stable on this medication, and psychiatric indication is correct. Lastly, we will examine whether patient characteristics influence the decision to either continue or discontinue SSRIs during pregnancy.

## Methods

### Data sources

For this population-based cohort study, 153,952 Dutch pregnancies were identified after probabilistic linkage between the Outpatient Pharmacy Database of the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). PHARMO is a dynamic cohort of participants that includes drug-dispensing records from community pharmacies of approximately 25% of the Dutch population (Herings et al. 1992). The pharmacies and their populations are generally accepted as representing outpatient drug prescription practice. As part of its national statistical responsibility, the Dutch government every year issues a "zip code-SES" conversion table, which is used for civil and research purposes. This SES-proxy appears a fairly accurate individual SES proxy. The PRN is a national registry that contains validated and linked data from midwives, gynaecologists, general practitioners and paediatricians on 95% of all pregnancies with a minimal gestational age of 16 weeks. More information on these databases and the probabilistic linkage can be found in Supplement 1. All pregnancies with a delivery date between January 1999 and December 2014 were included. To be able to define drug dispensing in the 12-month period before conception and 12 months after delivery, women needed to be registered in the community pharmacy database of the PHARMO Database Network for both of these 12-month periods.

### Drugs of interest

All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology n.d.). ATC codes of SSRIs start with N06AB (further defined onto the fifth level) and include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The SSRI drug-dispensing data contained the following information per dispensing: timing of dispensing (before, during or after pregnancy, based on dispensing date), regimen and quantity dispensed. For all other drugs, information was available on second ATC level, with timing only (before, during or after pregnancy). Only outpatient drug data are reported. Note that inpatient drug provision is exceptional, limited to pregnant patients who for other reasons are hospitalised for a longer period.

### Analysis

Women were defined as user of a SSRI during one of the three phases (12 months leading up to pregnancy, during pregnancy and 12 months after pregnancy) if a dispensing was recorded of at least 28 days duration, for a given phase. For trend analysis, data was grouped into 2-year periods (based on year of delivery) and the chi-square test for trends was used.

From the available data on use and pregnancy duration/delivery, we defined the following seven mutually exclusive patterns: (1) women who used SSRIs before pregnancy only; (2) women who used SSRIs both before and during pregnancy; (3) women who used SSRIs before, during and after pregnancy; (4) women who used SSRIs during pregnancy only; (5) women who used SSRIs both during and after pregnancy; (6) women who used SSRIs after pregnancy only and (7) women who used SSRIs before and after pregnancy, but not during (recidivist). Percentages of each group were calculated

per 2-year time period, allowing to test whether dispensing pattern changed, in particular related to the introduction of the guideline (2012).

To examine the association between general patient characteristics and continuation of SSRIs during pregnancy, only data of women using SSRIs in the year before pregnancy (women from the patterns 1, 2, 3 and 7) were used. Characteristics studied were year of delivery, parity, socio-economic status (based on data per zip code from the Central Bureau of Statistics (CBS), subdivided into low, middle and high), co-dispensing of psycholeptics (ATC code N05, including antipsychotics, anxiolytics, hypnotics and sedatives) and number of other co-medications (sum of all other pharmacy registered dispensed drugs, excluding SSRIs and psycholeptics) in the year before pregnancy. First, we determined univariable associations between the dependent variable and all the independent variables. Variables with a $p$ value $< 0.10$ were entered into a multivariable logistic regression model. Independent variables with a two-sided $p$ value $< 0.05$ in the multivariable model were defined as statistically significant. All associations were expressed as adjusted odds ratios (ORs) with the respective 95% confidence intervals (95% CIs). Statistical Package for Social Sciences (SPSS) version 25.0 was used.

## Results

A total of 153,952 pregnancies in the Netherlands with a delivery date between January 1999 and December 2014 were identified, with their associated dispensing data. Mean maternal age at delivery was 31 years, and socio-economic status was low in 28%, middle in 34% and high in 38%. Of these 153,952 pregnancies, 7284 (4.7%) used SSRIs in one or multiple phases. Mean maternal age at delivery for these pregnancies was similar (31 years), and socio-economic status differed slightly (shift to lower SES), with SES low in 35%, middle in 33% and high in 32% ($p < 0.01$). A short duration dispensing (< 28 days) was present in 536 (0.35% of all) women in the year before pregnancy, in 63 (0.04%) women during pregnancy and in 260 (0.17%) women in the year after pregnancy. These 759 cases were excluded from analysis.

### Dispensing patterns over time

Table 1 shows SSRI dispensing rates in the year before pregnancy, during pregnancy and in the year following pregnancy. Dispensing rate is highest in the year before pregnancy (e.g. 3.9% in 2013/2014) and lowest during pregnancy (e.g. 2.1% in 2013/2014). A significant rise over the years can be observed for all phases (before pregnancy, chi-square for trend = 48.411, $p < 0.001$; during pregnancy, chi-square for trend = 141.735, $p < 0.001$; after pregnancy, chi-square for trend = 10.540, $p = 0.001$), with the largest increase during pregnancy. The guideline introduction in 2012 did not interrupt this gradual increase.

Figure 1 shows starting and stopping patterns of SSRI use, comparing 2-year groups. The figure visualises the seven groups as mentioned in the methods. In the early years of our cohort, a minority of women using SSRIs in the year before pregnancy continued SSRIs during pregnancy (19% in 1999/2000), while after 2012, this percentage increased substantially; 46% continued their medication (chi-square for trend = 25.256, $p < 0.001$) (Fig. 2). The percentage of women initiating medication during pregnancy remains constant (0.27% in 1999/2000 and 0.28% in 2013/2014). A small proportion (17.6% overall) of women who discontinued SSRIs during pregnancy restarts SSRIs postpartum ("recidivist," pattern 7). Finally, the percentage of women who initiated SSRIs postpartum (pattern 6) decreased from 1.08% in 1999/2000 to 0.91% in 2013/2014. No obvious change in trend is visible after introduction of the guideline.

Concomitant use of psycholeptics was highly prevalent: Of the 5316 women using SSRIs in the year before pregnancy, 44.6% also used psycholeptics in that year. A mean number of 4.0 (SD 2.7) other co-medications were used in the year before pregnancy by this group (Table 2).

Table 3 shows, through a multivariable model, that several patient characteristics were independently associated with the decision to continue SSRI use. A low SES was related to decreased odds of continuation (OR 0.87, 95%CI 0.75–1.00) while a higher parity increased the odds of continuation with 15% per additional pregnancy (OR 1.15, 95%CI 1.09–1.21, $p < 0.01$). Specifically, the concomitant use of psycholeptics halved the probability of continuation of SSRI use during pregnancy (OR 0.50, 95%CI 0.43–0.55, $p < 0.01$). Generally, a more recent delivery increased the odds of continuation with 10% per calendar year (OR 1.10, 95%CI 1.08–1.11, $p < 0.01$);

### Individual drugs

Of the six SSRIs dispensed, combining all years, paroxetine was the most frequently dispensed, accounting for 42.3% in the year before pregnancy, 41.3% during pregnancy and 46.0% in the year following pregnancy. However, a significant change was observed (Fig. 3). Over time, the absolute number of paroxetine dispenses decreased steeply (except during pregnancy), as did the share of this particular SSRI among users more generally. Reversely, citalopram and sertraline showed an increase over time. Still, paroxetine was the most often dispensed SSRI in 2013/2014.

Of the 1986 women who used SSRIs in the year before pregnancy (all years combined) and who continued medication during pregnancy, 127 women (6.4%) switched from

**Table 1** Number of deliveries in which the women received a dispensing for a selective serotonin reuptake inhibitor (SSRI) in the year before pregnancy, during pregnancy or in the year following pregnancy, per 2-year group based on delivery date

| | Total number of deliveries | SSRI dispensing during: | | |
|---|---|---|---|---|
| | | The year before pregnancy (%) | Pregnancy (%) | The year following pregnancy (%) |
| 1999/2000 | 6172 | 170 (2.8) | 50 (0.8) | 133 (2.2) |
| 2001/2002 | 11,625 | 386 (3.3) | 118 (1.0) | 292 (2.5) |
| 2003/2004 | 14,201 | 437 (3.1) | 181 (1.3) | 388 (2.7) |
| 2005/2006 | 20,684 | 639 (3.1) | 276 (1.3) | 521 (2.5) |
| 2007/2008 | 28,231 | 935 (3.3) | 425 (1.5) | 742 (2.6) |
| 2009/2010 | 28,220 | 987 (3.5) | 462 (1.6) | 764 (2.7) |
| 2011/2012 | 22,652 | 906 (4.0) | 493 (2.2) | 681 (3.0) |
| 2013/2014 | 22,167 | 856 (3.9) | 461 (2.1) | 677 (3.1) |

SSRI at some point before, during or after pregnancy with no time trends being present (Table 4).

## Discussion

This large 16-year population-based study shows a general increase of SSRI use throughout pregnancy and beyond. A substantial change of practice towards more continuation during pregnancy was present, initiated already before introduction of the 2012 guideline. The dominance of paroxetine as SSRI of choice decreased. The latter change is a change in general preference, as switching between specific SSRIs is rare (6.4%). Higher parity increased the continuation rate, while low SES and concomitant use of psycholeptics substantially decreased the continuation rate.

Two Dutch author groups previously reported on older and smaller samples. Ververs described the experience of a cohort of 29,005 deliveries between January 2000 and July 2003, which was made available from one healthcare insurance company (Ververs et al. 2006). Here, 2.2% of women used SSRIs before pregnancy, with a decrease to 1.4% in the third trimester and an increase to 2.3% in the post-delivery period. Bakker et al. reported on a cohort of 14,902 pregnancies with deliveries between 1995 and 2004 available from the Interaction Database (IADB.nl) (Bakker et al. 2008). Over these years,

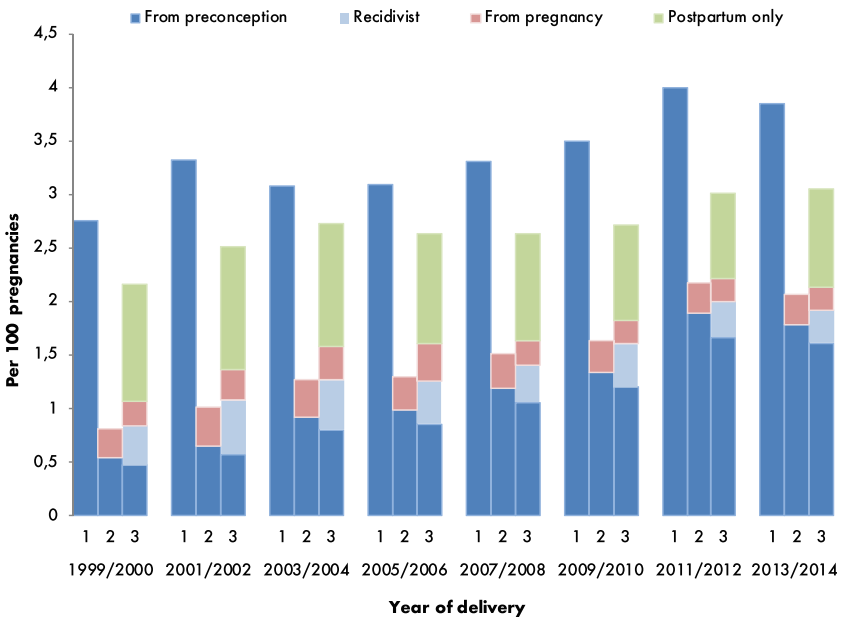


**Fig. 1** Selective serotonin reuptake inhibitors (SSRIs) perinatal dispensing rate per time period of interest per 100 pregnancies in the Netherlands, 1999–2014. 1 = the year before pregnancy, 2 = during pregnancy, 3 = the year after pregnancy. Complete data on all three phases was available for all women and thus the number of women at risk for each bar (1, 2 and 3) per 2 years is comparable. For example, a woman with a delivery date in 1999, who took SSRIs during all three phases (before, during, after) is represented in blue in all three bars (1, 2, 3) of the 1999 column. The dark blue bars represent the women that used their SSRI since the year before pregnancy. The pink and green bars represent the women that did not use SSRIs in the year before pregnancy but started using them during or after pregnancy respectively. The light blue bar represents those women that used SSRIs before pregnancy, discontinued during pregnancy, but restarted in the year after pregnancy


**Fig. 2** Percentage of women with selective serotonin reuptake inhibitor (SSRI) dispensing in the year before pregnancy continuing during pregnancy in the Netherlands, 1999–2014. Dotted lines represent the 95% confidence intervals

the exposure rate to SSRIs in the year preceding delivery increased from 1.2 to 2.9%. The data on the early years of our cohort fits to these observations and show that the growing trend has persisted 10 years beyond 2004. Research among the general Dutch population within the age category of 25 to 49 years (thereby including our target population) also reported an increase in SSRI use from around 2.5% in 1998 to 4.0% in 2004 (Bijlsma et al. 2014). A recent cohort study examined SSRI prescription in several European countries over the years 2004 to 2010. Prescription rates before, during and after pregnancy in our study were comparable to Denmark (4.1%, 2.3% and 4.1% respectively) and Italy (4.4%, 1.6% and 2.4% respectively), but prescription rates in the UK were considerably higher with 8.8 to 9.6% of women using SSRIs in the year before pregnancy (Charlton et al. 2015). Compared to the USA, where SSRI prescription rates during pregnancy increased from 2.9% in 1999 to 10.2% in 2003, prescription rates in European countries are low (Cooper et al. 2007).

A trend towards more continuation is observed over the years, without an obvious change in trend after introduction of the 2012 continuation guideline (NVOG 2012). As stated by this guideline, the recommendation to continue is a consequence of insufficient evidence on the benefits and risks to stop SSRI use, with or without non-pharmacological alternatives. Part of that is the absence of valid data on depression relapse after discontinuation. We interpret the low prescription rates in the Netherlands relative to other countries, such as the USA, as a higher prescription threshold, i.e., we assume that Dutch women with an SSRI prescription have a more severe psychiatric disorder. As this generally implies an increased risk of relapse, the continuation of SSRIs during pregnancy is even more justified. The alternative explanation is that severe psychiatric disorders, requiring pharmaceutical treatment, are more prevalent in other countries than in the Netherlands, although it is unlikely for this to fully explain the difference in SSRI prescription rates (Lim et al. 2018). We were surprised by the size of concomitant use of psycholeptics, as such drugs are universally associated with severe psychiatric disease. Their use halves the probability of continuation of SSRI use during pregnancy. The guideline does not address the issue. We hypothesise self-tapering by the women is responsible, as they may fear a cumulative detrimental effect on the unborn baby from multiple psychotropic medication; by self-tapering such women may think this benefits child outcome. Final interpretation of this interaction pattern requires more data, e.g. on the severity of underlying disease, length of medication use and previous discontinuation attempts and preferably interview data, both with the patients in question as well as associated caregivers guiding treatment decisions. A higher parity was associated with increased odds on continuing medication. This could be among others explained by the correlation of parity with age. A higher parity could point to a longer duration of psychiatric disease and/or longer duration of antidepressant treatment,

**Table 2** Characteristics of all women with SSRI use ($n = 7284$) before, during and/or after pregnancy and of women with SSRI use ($n = 5316$) in the year before pregnancy

| | Full SSRI sample | Women with SSRI use before pregnancy |
|---|---|---|
| Age in years, mean (SD) | 31.5 (4.7) | 31.5 (4.8) |
| Socio-economic status | | |
| Low | 2451 (33.6) | 1713 (32.2) |
| Middle | 2420 (33.2) | 1816 (34.2) |
| High | 2371 (32.6) | 1759 (33.1) |
| Concomitant use of psycholeptics, yes (%) | 2729 (37.5) | 2369 (44.6) |
| Number of co-medications, mean (SD) | 4.0 (2.7) | 4.0 (2.7) |

**Table 3** Univariable and multivariable associations between patient characteristics and continuing pre-conceptive selective serotonin reuptake inhibitor (SSRI) use during pregnancy. aOR = adjusted odds ratio, CI = confidence interval

| | Univariable outcome | | Multivariable outcome | |
|---|---|---|---|---|
| | cOR (95%CI) | *p* value | aOR (95%CI) | *p* value |
| Year of delivery | 1.10 (1.08–1.12) | < 0.01 | 1.10 (1.08–1.11) | < 0.01 |
| Parity | 1.15 (1.09–1.22) | < 0.01 | 1.15 (1.09–1.21) | < 0.01 |
| Socio-economic status | | | | |
| Low | 0.86 (0.75–0.98) | 0.03 | 0.87 (0.75–1.00) | 0.05 |
| High | 0.99 (0.87–1.13) | 0.88 | 0.97 (0.84–1.11) | 0.64 |
| Concomitant use of psycholeptics | 0.47 (0.42–0.53) | < 0.01 | 0.50 (0.43–0.55) | < 0.01 |
| Number of co-medications | 0.98 (0.96–1.00) | 0.03 | 1.00 (0.98–1.02) | 0.92 |

which in turn might lead to an increased perceived dependence on antidepressant treatment (Singh et al. 2016). Another explanation could be that multiparous women with previous healthy infant(s) under SSRI use are more convinced of the safety of SSRI use during pregnancy and are therefore less likely to discontinue. Third, higher parity could mean a more stressful environment for the woman, thus contributing to the decision to continue medication.

There has been a major shift in specific SSRIs dispensed over the years, with paroxetine losing its popularity. This may be a reflection of evidence showing a higher rate of negative birth outcomes in paroxetine use compared to the other SSRIs (Alwan et al. 2007; Bakker et al. 2010; Berard et al. 2007; Cole et al. 2007; Louik et al. 2007; Nakhai-Pour et al. 2010; Wurst et al. 2010). Overall, paroxetine remained the most frequently dispensed SSRI, while a population-based study from Denmark, Iceland, Norway and Sweden showed paroxetine was the least prescribed SSRI in the period of 2008 to 2012 (Zoega et al. 2015).

Evidence on the risk of relapse of depression when discontinuing medication during pregnancy is insufficient. The first randomised controlled trial is being executed at the moment

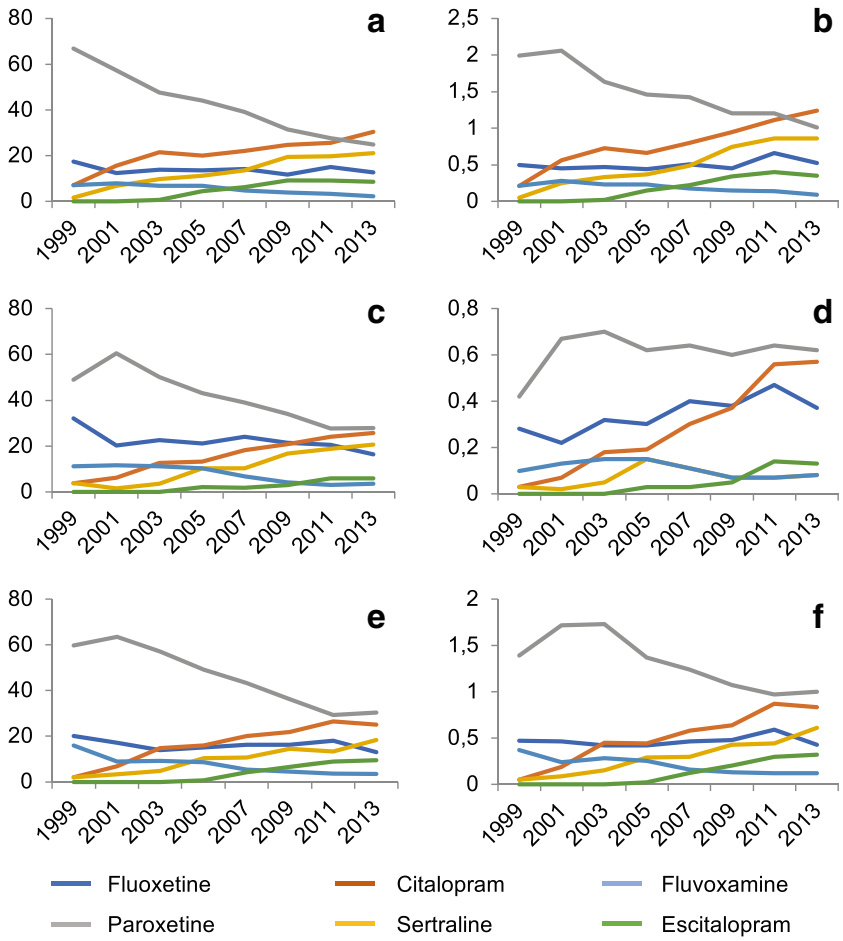


**Fig. 3** Relative and absolute dispensing rates per specific selective serotonin reuptake inhibitor (SSRI) before, during and after pregnancy in the Netherlands, 1999–2015. **a** Relative SSRI dispensing in the year before pregnancy. **b** Absolute SSRI dispensing in the year before pregnancy. **c** Relative SSRI dispensing during pregnancy. **d** Absolute SSRI dispensing during pregnancy. **e** Relative SSRI dispensing in the year after pregnancy. **f** Absolute SSRI dispensing in the year after pregnancy. Each year represents two calendar years

**Table 4** Specific SSRI's used before and after switch in women using SSRIs in the year before pregnancy and continuing SSRIs during pregnancy and switching at some point before or during pregnancy. Numbers sum up to more than the number of women due to multiple SSRIs used or multiple switches

| | SSRI used before switch, *n* (%) | SSRI used after switch, *n* (%) |
|---|---|---|
| Citalopram | 30 (22.2) | 34 (21.1) |
| Escitalopram | 10 (7.4) | 9 (5.6) |
| Fluoxetine | 11 (8.1) | 27 (16.8) |
| Fluvoxamine | 5 (3.7) | 12 (7.5) |
| Paroxetine | 31 (23.0) | 41 (25.5) |
| Sertraline | 48 (35.6) | 38 (23.6) |

(Molenaar et al. 2016), but so far, only two naturalistic studies report on relapse rates in women continuing or discontinuing antidepressants during pregnancy (Cohen et al. 2006; Yonkers et al. 2011). Where the first study reported a significant increased risk of relapse in women who discontinued their medication compared to women continuing medication (86 vs. 26%), the second study did not find a significant influence of antidepressant discontinuation on relapse risk (16% overall). In our current study, only a small proportion of women restarted medication after discontinuation during pregnancy, which may reflect the relapse rate of the psychiatric disorder.

## Strengths and limitations

The size and composition of the Outpatient Pharmacy Database is a major strength of this study. It includes representative data on approximately 25% of the Dutch population, thereby allowing for fairly good estimates on the level of the Dutch population. Data was available from a year before conception until the end of the year following pregnancy. An accurate conception date could be obtained from the PRN database based on ultrasound or the last menstrual period, and the exact delivery date was also present in the PRN database. However, even this dataset had its limitations. Coverage of all pregnancies was less than 25% as linkage could not be established in all cases, potentially reducing representativeness. Exact timing of drug dispensing for this study was defined according to before, during and after pregnancy, enabling us to rule out the possibility that drugs dispensed just before pregnancy were still being used in the first trimester of pregnancy and so on. For some drug dispensing, an unknown ATC code was registered, thereby potentially missing a small amount of SSRI dispensing leading to underreporting of SSRI dispensing among the target population. Besides defining use in one of three phases by a prescription for a duration of 28 days, we did not take overall length of use into account.

A limitation of prescription registry data is that actual use may be less (non-compliance), or more (external sources of medication, shelf medication). Non-compliance is the most likely weakness, due to an increasing societal and professional reluctance to take/prescribe drugs during pregnancy, and psychotropic drugs in particular (Lupattelli et al. 2015). In this study, we assume the likelihood of underestimation to be very small. Last, information on pregnancies that ended before a gestational age of 16 weeks was excluded in our study as the PRN database only contains information of pregnancies of ≥ 16 weeks of gestation. However, SSRIs do not seem to increase risk of miscarriage (Andersen et al. 2014) and in addition, patterns examined in this study would not be affected.

## Conclusion

For more than a decade, perinatal SSRI use shows a steady increase. Rise is most prominent during pregnancy, by the combined effect of a general rise in SSRI use in all patients (possibly as a result of a rise in depression), and a change towards continuation rather than discontinuing when women get pregnant. Despite a substantial shift in drug preference, paroxetine is still most commonly used. Switches are rare. In view of the demonstrated impact of uncertainty regarding effectiveness and safety of SSRIs in pregnancy, future research should involve more detailed outcome research of SSRIs as it is and research into viable alternatives (drug/non-drug) for the use of SSRIs in pregnancy.

**Acknowledgements** The authors would like to thank all the healthcare providers contributing information to the PHARMO Database Network. Additionally, they would like to thank the PHARMO Institute (Mrs. E. Houben, Mr. R. Herings) and the Netherlands Perinatal Registry (Mrs. C. Hukkelhoven) for providing access to their database, and for the support to obtain permission for use of the datasets.

**Funding** The dataset was obtained with the support of the Department of Public Health of the Erasmus MC, Rotterdam, the Netherlands and the Psychosomatics Working Group in Obstetrics and Gynaecology (WPOG; www.wpog.nl).

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

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# Antidepressant use During Pregnancy: Knowledge, Attitudes, and Decision-Making of Patients and Providers

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**Introduction:** Despite the risks associated with untreated perinatal depression and anxiety, both patients and clinicians are less likely to follow evidence-based guidelines including the use of antidepressants during pregnancy. The aim of this integrative review was to describe the perspectives of both patients and prescribing health care providers regarding the use of antidepressants during pregnancy.

**Methods:** We performed a literature search in PubMed, CINAHL, ProQuest Central, and PsychINFO. Inclusion criteria were English language, original peer-reviewed research published within the previous 10 years that described perspectives regarding the use of antidepressants of pregnant patients or prescribing providers during pregnancy. Studies were excluded if their focus was on screening practices, treatment guidelines, or evaluation of decision support tool; medication or treatment broadly; bipolar disorder or serious mental illness; or they did not provide patient or provider perspective. This review was limited to professionals with scopes of practice that include prescriptive authority (eg, physicians, advanced practices nurses, midwives). Included articles were critically appraised and read in an iterative process to extract methodological details and synthesize findings.

**Results:** Nineteen studies met criteria for inclusion and varied by design, sample, and quality. Together, the reviewed articles suggest that patients and prescribing providers hold a range of beliefs regarding the safety of antidepressant during pregnancy. Patients and providers appear to value different sources of information and varied in awareness of the negative impacts of untreated depression and anxiety during pregnancy. Many patients report dissatisfaction with available information and distress throughout the decision-making experience. Notably, patients and providers had incongruent perceptions of the others' experience.

**Discussion:** Inconsistencies between knowledge, attitudes, and decision-making highlight the need for improved dissemination of evidence-based treatments and support increased training for psychopharmacology during pregnancy. Efforts to reduce patient distress regarding their decisions, such as adequate time and information, are indicated.
J Midwifery Womens Health 2022;67:332–353 

*Keywords:* pregnancy, depression, anxiety, antidepressants, knowledge, attitudes, integrative review

## INTRODUCTION

Pregnancy is a high-risk period for the onset or exacerbation of many mental health concerns, including anxiety and depression, which occur in approximately 20% of pregnancies.[1–4] Left untreated, anxiety and depression are associated with adverse effects for pregnant persons, newborns, and infants such as low birth weight, prematurity,[2,4–6] poor infant attachment, low maternal confidence, postpartum depression, and lower rates of breastfeeding.[7,8] Suicide, a potential outcome of untreated depression, is a significant cause of pregnancy-associated death.[9] Depression during pregnancy is also associated with poor self-care and higher rates of substance and alcohol use.[10,11]

Antidepressants and evidence-based psychotherapies are considered the first-line treatments for depression and anxiety.[12] Although some concerns persist about the safety of antidepressants during pregnancy, the most recent guidelines from the British Association for Psychopharmacology recommend against routine discontinuation during pregnancy without consideration of specific risks and benefits for that individual.[13] The American Psychiatric Association and American College of Obstetricians and Gynecologists conclude that psychopharmacology may be necessary for some pregnant patients.[14] Multiple metanalyses support the relative safety of many antidepressants, including selective serotonin reuptake inhibitors (SSRIs), during pregnancy.[15] Antidepressants are often indicated when depression and anxiety have been refractory to psychotherapy alone.[16]

Pregnant people may experience difficulty accessing or maintaining mental health care,[17] and some report being advised not to become pregnant while taking antidepressants or to discontinue them when pregnant.[17,18] Use of antidepressants drops by 80% during pregnancy compared with preconception and postpartum periods.[19] Only 8% to 13.8%

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 1526-9523/09/$36.00 doi:10.1111/jmwh.13366

## Quick Points

- Many patients endorse uncertainty and distress about the use of antidepressants during pregnancy and require support, reassurance, and access to adequate information and time during treatment planning.
- Although some prescribing health care providers describe themselves as knowledgeable and confident in the use of antidepressants during pregnancy, many overestimate the teratogenic risks of antidepressants compared with evidence-based guidelines.
- Knowledge, attitudes, and decision-making regarding the use of antidepressants during pregnancy varied among and between patients and providers.
- Some patients perceive providers to be uncomfortable or unwilling to discuss antidepressants during pregnancy and may not disclose their concerns for fear of judgment.

of pregnant women who meet the diagnostic criteria for depression report antidepressant use.[20] In contrast, 25% to 40% of adult women with depressive symptoms reported antidepressant use according to the most recent relevant National Center for Health Statistics bulletin.[21] Although they were similar in their symptom severity at baseline, pregnant woman who declined or discontinued antidepressants had higher anxiety and depression scores at follow-up than women who initiated or continued antidepressants.[22] Pregnant women who discontinued antidepressants, whether on their own or at the recommendation of a health care provider, were more than 60% more likely to experience a recurrence of depression symptoms compared with those who remained on medication.[23]

Most mental health care during pregnancy is provided in primary and prenatal care settings.[24] Therefore, midwives, obstetrician-gynecologists, advanced practice nurses, and other physicians in those settings are well positioned to support collaborative decision-making through careful consideration of individual risks and benefits of treatment compared with nontreatment for depression and anxiety in pregnancy. Despite evidence-based treatments and clinical guidelines, health care providers are less likely to screen patients and follow guidelines for depression and anxiety treatment during pregnancy. Many lack knowledge regarding the adverse effects of untreated depression and anxiety during this period.[24] The reasons for these practice patterns are not well understood. Discrepancies between recommendations and practice leaves many pregnant individuals at risk for untreated depression, anxiety, and related adverse effects.

The aim of this review was to describe the perspectives of both patients and prescribing providers regarding the use of antidepressants for the treatment of depression and anxiety during pregnancy through the critical appraisal and synthesis of the existing literature.

## METHODS

### Design

The integrative review methodology described by Whittemore and Knafl[25] including the 5 stages of problem identification, literature search, data evaluation, data analysis, and presentation of results was used for this review. The review was limited to professionals with scopes of practice that include prescriptive authority (eg, physicians, advanced practice nurses, midwives).

#### *Literature Search*

A systematic search of PsychINFO via Ovid, MEDLINE via PubMed, ProQuest Central, and CINAHL was conducted between March 2021 and August 2021. Three concepts were used in the search: *pregnancy*, *psychopharmacology* for depression or anxiety, and *perspectives* of pregnant patients or prescribing providers. Perspectives included multiple search terms related to subjective experience (eg, knowledge, beliefs, attitudes, opinions, decision-making, decision conflict) to capture as many relevant results as possible. Subject headings, Medical Subject Headings, database-specific headings, keywords, synonyms, truncation, and Boolean phrases were used. A health sciences librarian assisted with amending search specifications to generate the optimal search strategy for each database.

Inclusion criteria included English language, original research published in peer-reviewed journals describing perspectives of pregnant patients or prescribing providers (eg, physicians, advanced practice nurses, midwives) regarding the use of antidepressants during pregnancy. A limit of 10 years, 2011 to 2021, was applied to the initial search in an effort to maintain clinical relevance in consideration of psychopharmacological developments and evolving prescribing trends. The terms *pregnant people* and *patients* were used to include persons across the gender spectrum with the capacity for pregnancy. However, when discussing specific results of articles reviewed, we use the terminology (eg, woman, pregnant women) used by the original authors.

Studies were excluded if they did not include patient or provider perspective or exclusively focused on screening practices, treatment guidelines, or evaluation of a decision support tool; medication or treatment of depression or anxiety broadly (eg, not related to pregnancy); or bipolar disorder and other serious mental illnesses. A synopsis of this search is presented in Figure 1. To ensure the inclusion of articles related to both patients and providers, quality was not used as an inclusion or exclusion criterion but was considered in the analysis.

The initial search returned 1056 articles which were imported to Covidence Systematic Review, a web-based program designed to facilitate screening and data extraction.[26] After duplicate results were removed, 846 titles and abstracts were

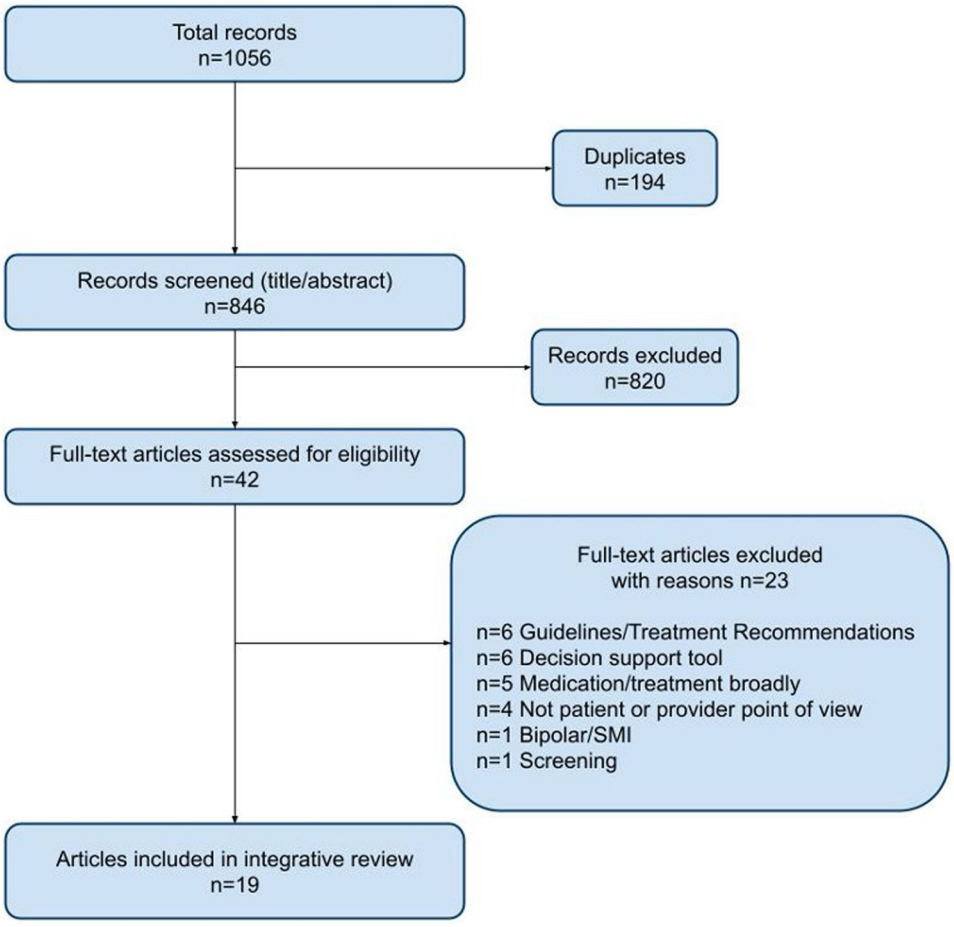


**Figure 1. Study Selection and Search Outcomes**

Abbreviation: SMI, serious mental illness.

screened for relevance and 42 articles were identified as appropriate for full-text review. Nineteen articles, describing 19 unique studies, met full criteria for inclusion. A hand search of cited references did not identify any additional articles meeting inclusion criteria.

### *Data Evaluation and Quality Appraisal*

Each included article was read multiple times in an iterative process to evaluate quality, extract methodological details, and synthesize findings. Articles were critically appraised using Joanna Briggs Institute Critical Appraisal tools[27] for observational studies and quantitative aspects of mixed-methods designs and Whittemore et al validity criteria for qualitative designs.[28] Strengths and weaknesses of each article are summarized in Supporting Information: Table S1. Study design, aims, sampling strategy, sample characteristics, methods, and key results were extracted for analysis. Studies were classified as having a patient or provider sample and by the methodology used, then reviewed to identify key findings and recurring domains. Extracted data were organized in 3 predominant domains: knowledge, attitudes, and decision-making. Extracted data are summarized and presented in further detail for patient perspectives in Table 1 and provider perspectives in Table 2.

## RESULTS

### Data Analysis

### *Study Characteristics*

Of the 19 studies, 4 were defined by their authors as qualitative, 7 were mixed-methods, and the remaining 8 used quantitative methodologies. The majority of studies relied on study-specific surveys or questionnaires designed by the authors.[22,29–42] Focus groups were used in one study,[43] and in-depth semistructured interviews were used in 4 studies.[20,22,41,44]

Eight studies considered the perspective of patients, 10 focused on health care providers, and one included both groups. Obstetrics and gynecology (8), primary care (5), and psychiatry (4) were the most frequently included medical specialties. All provider samples included physicians, 3 included registered or advanced practice nurses, and 2 included other types of staff members. No study specifically identified midwives as participants. Six articles noted the inclusion of students or trainees. Demographic characteristics reported for both groups included age, gender or sex, race or ethnicity, education, and marital status. Characteristics specific to providers included professional experience, practice characteristics, and experience with depression. Mental health

**Table 1. Presentation of Results: Summary of Patient[a] Perspectives Regarding the Use of Antidepressants During Pregnancy**

| Author (year) *Country* Title | Study Aim | Sample | Domains and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Mulder et al (2012)[42] *Canada* Negative impact of nonevidence-based information received by women taking antidepressants during pregnancy from health care providers and others | Determine impact of information, advice, comments from family, media and HCP | 78 women who continued treatment; 16 women who discontinued treatment recruited through random recontact from parent study of women taking antidepressants prior to pregnancy | Knowledge; sources of information; opinion | Semiqualitative, mixed-method; 67-item questionnaire developed by authors, ~30 min to complete, unclear format. Demographics: education, marital status, race, income, depression severity | Most spoke to additional providers; 75% sought information from internet sources; 30% were concerned with stigma from friends or family; more of those who continued treatment found their provider to be reassuring (75%) compared with those who discontinued (50%); 13%-14% believed the provider was uncomfortable discussing topic; providers were more reassuring than friends or family; negative information was recalled more often in more detail; 20% were upset by comments from others; most continued to feel guilty or worry despite reassurance; those that discontinued treatment did not receive more negative information |
| Battle et al (2013)[20] *United States* Perinatal antidepressant use: understanding women's preferences and concerns | Characterize women's experience with decisions about antidepressants during pregnancy, assess treatment preferences | 61 pregnant women with and without depression, subset of larger study | Attitudes; concern; beliefs; decision-making | Mixed-methods; in-depth interview, questionnaire, decisional-conflict scale. Demographics: age, marital status, race, pregnancy history, socioeconomic factors | Preference for nonpharmacological treatment; high degree of uncertainty reported; more severe symptoms associated with higher decision conflict; higher uncertainty associated with no treatment or inconsistent treatment; some with a positive effect from antidepressants in the past and had positive attitudes toward treatment others considered antidepressants a "last resort" |

(*Continued*)

**Table 1. (Continued)**

| Author (year) *Country* Title | Study Aim | Sample | Domains and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Misiri et al (2013)[22] *Canada* Factors impacting decisions to decline or adhere to antidepressant medication in perinatal women with mood and anxiety disorders | Identify factors that impact the decision to adhere or decline antidepressants during pregnancy | 50 women with moderate-severe depression, screened at clinic intake, offered antidepressant treatment during pregnancy: 30 who accepted antidepressant treatment; 20 who declined antidepressant treatment | Attitudes; concern; beliefs; decision-making | Mixed-methods, cross-sectional; questionnaire, self-report, verbal explanation of treatment decision, recorded by research assistant. Demographics: age, race, ethnicity, income, education, marital status, mental health history | Divergent illness course for those who accepted or declined antidepressants, with higher anxiety and depression scores at follow-up among those who declined; those who declined had less insight into illness severity, more concern for fetal risks, low confidence in medication; those that accepted antidepressants had more positive attitudes of depression and of medication |
| Walton et al (2014)[41] *Canada* Decisional conflict among women considering antidepressant medication use in pregnancy | Examine decision-making regarding the use of antidepressants during pregnancy among pregnant women | 40 (survey) and 10 (interview of high decisional-conflict subgroup) newly pregnant women considering antidepressant, recruited at mental health clinic visit | Knowledge; sources of information; attitudes; concern; decision-making | Mixed-methods, cross-sectional; questionnaire, decisional-conflict scale, diagnostic interview for depression assessment, qualitative interview for women with high conflict scores, semistructured interview to assess barriers and facilitators. Demographics: age, marital status, whether born in Canada, income, education, pregnancy history, mental health history | Barriers: Emotional reactions: decision-making was upsetting, stressful for many; lack of information: quality of information was low or inconsistent, wish for long-term results; maternal health weighted against infant health: unclear of risks and benefits of treatment vs nontreatment; negative influence: unsupportive partners, friends or family, disagreement against patients' decision. Facilitators: Interpersonal support: decisions were easier with agreement and support. Symptom severity: major episode or relapse. Subspecialty care: access to specialist care |

(*Continued*)

**Table 1. (Continued)**

| Author (year) *Country* Title | Study Aim | Sample | Domains and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Bowman et al (2015)[40] *United States* Sources impacting pharmacological treatment for anxiety and/or depression during pregnancy | Identify sources of information used in decision-making by women during pregnancy concerning the used of antidepressants | 52 pregnant women within an academic medical center who had taken and antidepressant at some point during this pregnancy: 21 who continued treatment; 31 who discontinued treatment | Knowledge; sources of information; decision-making | Mixed-methods, survey; 29-item survey, completed in person at clinic site in ~10 min. Demographics: education, race, insurance status, smoking status | 27% who discontinued reported moderate-severe symptoms of depression at the time they discontinued medication; 44% of the sample named obstetrician as source for the best information; no relationship between type of provider consulted, education, or used of the internet and the decision to discontinue; women who did not speak with the child's father were nearly 4 times more likely to discontinue antidepressants; child's father and the internet provided the worst information |
| Nygaard et al (2015)[44] *Denmark* Balancing risk: a grounded theory study of pregnant women's decisions to (dis)continue antidepressant therapy | Explore how pregnant women with depression make decisions about the use of antidepressants during pregnancy | 8 pregnant women with depression currently taking or recently stopped taking antidepressants, recruited from clinical intake visit | Knowledge; sources of information; attitudes; concern; beliefs; decision-making | Qualitative, constructivist grounded theory; semistructured in-depth interview, development of interview guide with sensitizing concepts. Demographics: age, pregnancy history | Encountered information related to the risk of antidepressants during pregnancy from media or previous experience with antidepressants; impact of significant others: most identified partners, family, friends, and health professionals as supportive; used significant others to corroborate their understanding of mental health symptoms and acceptance of their decision; uncertain of safest decision for self and child; identification with role of mother as a protector of harm use to support decision to stop, continue, or resume antidepressant |

(*Continued*)

**Table 1. (Continued)**

| Author (year)<br>*Country*<br>Title | Study Aim | Sample | Domains and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Kothari et al (2019)[39]<br>*Australia*<br>Perceptions of pregnant women regarding antidepressant and anxiolytic medication use during pregnancy | Explore attitudes and decision of pregnant women concerning the use of antidepressants during pregnancy | 503 pregnant women recruited at first visit to maternity care clinic | Knowledge; sources of information; influences; attitudes; beliefs; decision-making | Quantitative, observation, survey; electronic questionnaire administered while waiting to see obstetrician, multiple choice, Likert scale, piloted by group of administrators, patients, and health care staff. Demographics: age, pregnancy history | 47 participants had been taking antidepressants at the beginning of pregnancy or stopped immediately prior; 68% chose to discontinue; general practitioners named as greatest influence with family and internet also named highly influential; obstetrician, television, newspapers, and magazine had low influence; many believed they did not have enough information or time for decision-making, and found information to be unclear or confusing; most common reasons for discontinuation were concern for side effects to newborn, health professional advice |
| Lemon et al (2020)[45]<br>*United States*<br>Treating anxiety during pregnancy: patient concerns about pharmaceutical treatment | Describe pregnancy women with anxiety's concerns about the use of antidepressants during pregnancy, compare these concerns with willingness to try antidepressants | 148 pregnant women recruited through online crowdsourcing site | Attitudes; concern; decision-making | Mixed-methods, cross-sectional survey; online survey forced choice, Likert scale, write-in opened ended formats; | Most frequent concerns: Global concern: worry that some harm will be caused to the child. General opposition: avoidance of all medication during pregnancy. Concern for long-term developmental effects for the child, and concern for side effects or long-term effect for the mother; willingness to consider antidepressants during pregnancy was associated with current mental health treatment |

Abbreviations: HCP, health care provider.
[a] For Price and Bentley (2013) see Table 2.

**Table 2. Presentation of Results: Summary of Provider Perspectives Regarding the Use of Antidepressants During Pregnancy**

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Kean et al (2011)[35] *Scotland* Antidepressants for mothers: what are we prescribing? | Investigate prescribing patterns of general practitioners for psychopharmacology during lactation and pregnancy | Nonrandom sample general practitioners in a hospital catchment area (32, 41%) | Attitudes; concern; confidence; reluctance; decision-making | Qualitative, internet and postal survey sent to all general practitioners within the catchment area, including demographics, response to 2 clinical vignettes, drug choice and rationale during pregnancy and lactation. Demographics: none | Most chose or avoided classes of medications rather than specific psychopharmacological agent; inconsistent responses, eg, 25% "avoided" all drugs, whereas 10% "preferred no drug at all" during pregnancy Inconsistent patterns, eg, fluoxetine was both the most preferred and most avoided answer during breastfeeding |
| Godbole et al (2011)[37] *India* A survey among psychiatrists regarding psychotropic drug use in reproductive age women | Understanding of knowledge, attitude, and practices of psychiatrists in the treatment of women during prenatal period and pregnancy | Nonrandom sample psychiatrists in Maharashtra, India (52, 80%) | Knowledge; sources of information; knowledge assessment; attitudes; confidence; reluctance; decision-making | Quantitative questionnaire; semistructured open-ended postal questionnaire, developed by authors, assess knowledge, practice patterns, beliefs and attitudes of psychiatrists in various settings and stages of career development. Demographics: none | 71% received some education regarding psychopharmacology during pregnancy, half would like more training in this area One-third did not identify which medications they would avoid; 22% report legal liability concerns; 56% consult resources to assist decision; years of practice not correlated with treatment decisions |

(*Continued*)

**Table 2.** (Continued)

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Bilszta et al (2011)[36] *Australia, Canada* Primary care physician's attitudes and practices regarding antidepressant use during pregnancy: a survey of two countries | Explore knowledge, attitudes, and practices in perinatal depression | Nonrandom sample Australian family practitioners recruited from training workshops regarding screening and treating depression (61, 79.2%); random sample Canadian general practitioners of every fourth provider in the Canadian Medical Directory in the Greater Toronto area (35, 31.5%) | Knowledge; attitudes; beliefs; concerns; beliefs; decision-making | Quantitative, anonymous survey; questionnaire developed by authors for the study. Australian arm administered in person; Canadian arm mailed. Self-administered survey with 3 aims (1) demographics (2) questions about attitudes and beliefs about antidepressant use during pregnancy and understanding of patients concerns (3) treatment decisions in response to a hypothetical clinical vignette. Likert-type answers to rate agreement with statements. Demographics: age, gender, mean years of practice, personal experience with depression | Provider similarities (Australian and Canadian); 60% and 72.4% would continue medication during pregnancy; 53.3% and 48.3% believe pregnant individuals should be treated differently; 74.6% and 82.1% encountered misinformation; 55% and 45.2% were concerned for legal liability for prescribing during pregnancy. Providers differences: 41.7% and 82.8% relatively safe for mother; 10% and 48% relatively safe for fetus; 33.3% and 57.1% confident providing advice regarding antidepressants during pregnancy; legal concerns more common for Canadian providers that discontinued (75%) than continued (48%) medications, whereas approximately half of both Australian providers who continued or discontinued expressed this concern |

(*Continued*)

**Table 2. (Continued)**

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Kean et al (2013)[38] *Scotland* Antidepressants for mothers: what are psychiatrists prescribing | Assess prescribing patterns and attitudes of hospital-based psychiatrists related to psychopharmacology during lactation and pregnancy | Nonrandom sample psychiatrists across stages of career development within a hospital system (68, 71.6%) | Attitudes; reluctance; decision-making | Qualitative, internet survey sent to all psychiatrists within a hospital system, including demographics, response to 2 clinical vignettes, assessment of confidence, experience, drug choice and rationale during pregnancy or lactation; comparison to existing guidelines for psychopharmacology during pregnancy. Demographics: none | Results generally congruent with evidence-based treatment guidelines; 63.2% rated confidence prescribing during perinatal period; however, many did not answer with drug choice or named only a class of medication; fluoxetine preferred during pregnancy; 22% would avoid paroxetine during pregnancy; 36.8% only reported the classes to avoid, which did not include the class that contains paroxetine; rationale for drug choice and sources of information varied between pregnancy and lactation periods |
| Byatt et al (2013)[43] *United States* Community mental health provider reluctance to provide pharmacology may be a barrier to addressing perinatal depression: a preliminary study | Assess provider and staff perceptions of barriers to accessing psychopharmacology treatment for depression during pregnancy | Purposeful sample of physicians and staff within a tertiary care center (28) | Knowledge; sources of information; reluctance; concern | Qualitative, focus group, grounded theory; 3 90-min focus groups of distinct staff types followed by an additional focus group including selected members of the first to review and refine initial findings, audio recorded, transcribed and reviewed for accuracy. Demographics: none | Barriers to care: reluctance to provide psychopharmacology to pregnant people by community mental health providers; lack of collaboration and communication; facilitators of care: increased communication; continuity of care; proposed solution: training community mental health providers |

(*Continued*)

**Table 2.** (Continued)

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Price and Bentley (2013)[34] *United States* Psychopharmacology decision-making among pregnant and postpartum women and health providers: informing compassionate and collaborative care women's health | Deepen understanding of decision-making and experiences among consumers and health care providers regarding psychopharmacology during pregnancy | Purposeful sample within 50 randomly selected academic medical centers in the United States, one per state, prescribing providers (88, 29%); nonrandom sample recruited through direct marketing on relevant websites, women who were pregnant or <2 y postpartum (83, 42%) | Attitudes; decision-making | Mixed-methods, electronic survey; Web-based survey to collect perceptions, personal experience, response to clinical vignettes. Forced and open-ended question formatting; demographics of providers: age, race, practice characteristics, provider type | Emphasis on potential benefits of psychopharmacology in bonding, role fulfillment, reduce stress, quality of life used to inform decision-making in both providers and women groups; providers anticipated more emphasis on social stigma than women expressed; fetal, infant, developmental effects, and breastfeeding concerns less prioritized by providers compared with women; lack of positive experience: 13% of providers and 27% of women endorsed no positive comments to describe communication |
| Cantilino et al (2014)[33] *Brazil, Argentina* Use of psychotropic medications during pregnancy: perception of teratogenic risk among physicians in two Latin American countries | Evaluate physicians' perceived risk of psychopharmacology use during pregnancy | Convenience sample of physicians of multiple specialties, nonrandom; 40 of each specialty (238, 98%); Argentina (118); Brazil (120) | Knowledge; knowledge assessment; concern; decision-making | Quantitative, survey; response rating the perception of teratogenic risk for different types of medications, including antidepressants, and degree of interest and knowledge in the topic. Answers compared across specialties and medication classes as well as with known rates of malformation as described in relevant literature at the time. Demographics: age, sex, date of graduation | 42.6% believed psychiatric medications were more harmful than other classes; perceived risks of psychopharmacology were overestimated by all specialties except psychiatry; obstetrician-gynecologists reported the least use of psychopharmacology during pregnancy; variable patterns of engagement with up-to-date information between specialties, 70.5% report reading relevant scientific material |

(*Continued*)

**Table 2.** (Continued)

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Yazici et al (2015)[32] *Turkey* Psychiatrists' attitudes toward psychopharmacologic treatments during pregnancy and lactation periods: a survey study | Evaluate attitudes and personal opinions of psychiatrists regarding the use of psychopharmacology during pregnancy and lactation | Nonrandom sample recruited from a closed, professional email group of psychiatrists across career stages (213, <10%) | Knowledge; attitudes; beliefs; decision-making | Quantitative, descriptive study using internet survey developed by authors, forced-choice format to assess treatment approaches and opinions as well as knowledge, engagement with current literature, and education. Demographics: stage of career, age, marital status | More likely to avoid starting medication, recommend discontinuing a medication, recommend alternative treatments, and seek higher level consultation during pregnancy compared with lactation periods; 73% would always or generally avoid psychopharmacology during pregnancy; 47% would always or generally recommend discontinuation during pregnancy; when drug treatment was considered necessary, psychiatrists reported higher agreement with "avoid pregnancy" than "avoid lactation"; 85% of psychiatrists state they know and apply appropriate guidelines during pregnancy and lactation either always or generally; 81% believed that they were able to provide patients with appropriate information during appointments; attitudes generally did not change based on self-identified knowledge level |

(*Continued*)

**Table 2. (Continued)**

| Author (Year)<br>*Country*<br>Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Gils et al (2016)[31]<br>*Denmark*<br>Perception of drug teratogenicity among general practitioners and specialists in obstetrics/gynecology: a regional and national questionnaire-based survey | Assess providers' perception of teratogenic risk of prescription drugs, including antidepressants | Nonrandom sample general practitioners in Southern Denmark (143, 18%); obstetrician-gynecologists in Denmark (138, 27%) | Knowledge; knowledge assessment; attitudes | Quantitative online questionnaire; anonymous, self-administered online questionnaire collection of demographics. Assess adherence to guidelines, and risk perception as compared to rates of background malformation in the population of 12 medications, including psychopharmacology. Demographics: none | Answers were similar between groups and existing literature, greater variation among general practitioners; general practitioners more likely to overestimate risk for citalopram and sertraline; both groups underestimated risk of retinoids and warfarin; results more closely aligned with known teratogenic risk than previous studies |

(*Continued*)

**Table 2.** (Continued)

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Taouk et al (2017)[30] *United States* Prenatal depression screening and antidepressant prescription: obstetrician-gynecologists' practices, opinions, and interpretation of evidence | Evaluate beliefs of obstetrician-gynecologists regarding screening and treatment of depression during pregnancy, including antidepressants | Nonrandom sample of 1000 ACOG obstetrician-gynecologists fellows (379, 37.9%). Subset of these provided care to pregnancy patients and answered psychopharmacology questions (288) | Knowledge; sources of information; attitudes; confidence; decision-making | Mixed-methods, cross-sectional survey; anonymous survey via participant preference of postal or electronic. Questions regarding screening and prescribing patterns, barriers, comfort, influences, opinions, use and interpretation of the literature. Demographics: membership, practice years, gender, location, practice details | Those with more comfort prescribing SSRIs were more likely to be female, have fewer years of practice, have a higher percentage of white and privately insured patients, have more frequent prescribing, and believe SSRIs were "not associated with elevated risk"; those that prescribe SSRIs more likely to counsel that risks of depression outweigh risk of medication and believe SSRIs were not associated with increased risk or were "relatively safe"; 74.4% "sometimes" or "usually or always" prescribed psychopharmacology and 22.0% rarely or never did; 78.1% were somewhat or very comfortable prescribing SSRI during pregnancy; 65.6% would continue an SSRI and 24.3% would recommend discontinuation; 35.8% would continue a non-SSRI and 20.8% would recommend discontinuation; 71.2% would avoid paroxetine; 6.2% would avoid sertraline |

(*Continued*)

**Table 2.** (Continued)

| Author (Year) *Country* Title | Study Aim | Sample (n , % response rate) | Domain and Subdomains | Design, Data Collection, and Analysis | Key Findings |
|---|---|---|---|---|---|
| Williams et al (2020)[29] *Australia* Prescribing antidepressants and anxiolytic medications to pregnant women: comparing perception of risk of foetal teratogenicity between Australian obstetricians and gynecologists, specialty trainees and upskilled general practitioners | Describe practice patterns related to prescribing antidepressants and anxiolytics during pregnancy | Nonrandom sample of obstetrics and gynecology fellows and trainees and general practitioners with specialized training recruited through professional interest group (545, 6.8%-12.9%) | Knowledge; knowledge assessment; attitudes; concern; confidence; decision-making | Observational cross-sectional national survey; 34-item questionnaire developed for study forced-choice format to assess attitudes about the use of psychopharmacology during pregnancy. Demographics: practice information | Total sample: overall, no specific interest in perinatal mental health, little involvement in relevant research, or engagement in conference or journals, reported low levels of concern about prescribing during pregnancy; agree more training would be helpful (71%); incorrectly labeled teratogenicity risk (22.3%); general practitioners: reported more concern about teratogens, predicted higher anxiety from patients, more time (15 min) discussing risks and side effects; initiated psychopharmacology (84.5%); confidence with their knowledge (57.6%); adequate training (56.1%); refer to mental health (5.3%); obstetrics and gynecology: less concern about teratogens, less time (5 min) discussing risks and side effects; initiated psychopharmacology (52.2%); confidence with their knowledge (44.2%); adequate training (29.0%); refer to mental health (48.8%) |

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; HCP, health care provider; SSRI, selective serotonin reuptake inhibitors

treatment history, employment, income and details regarding the current pregnancy were reported among patient groups. Specific demographics varied between studies and many reported no demographic data at all. In total, data were collected in 9 countries including the United States (6), Australia (5), Canada (2), Denmark (2), Scotland (2), Argentina (1), Brazil (1), India (1), and Turkey (1).

### *Terminology*

The terms from the above search strategy were used in the reviewed articles in a variety of ways. *Pregnancy* was used the most consistently. Although some studies included both pregnant and postpartum people, each article included decision-making during pregnancy either by questioning currently pregnant people or through asking hypothetical or retrospective questions of participants regarding mental health treatment choices during pregnancy.

*Depression and anxiety* were identified in numerous ways, ranging from patient self-identification, health record review, survey or assessment tool, in-depth clinical diagnostic interviews, or direct referral from a mental health provider. Therefore, *depression* and *anxiety* are not equivalently defined across studies, variously referring to the presence or absence of current symptoms, history, or diagnoses.

As intended by the inclusion criteria, all articles included some mention of antidepressants, either broadly by pharmacologic category or by specific medication name. The treatment of depression or depressive symptoms was identified in 13 articles, and 5 articles addressed anxiety. The remainder framed their investigation regarding mental health treatment broadly (4) or included medications used to treat mental health conditions among other classes of medication (1).

To understand patient and provider *perspectives*, this review included studies that variously assessed knowledge, perceptions, beliefs, attitudes, opinions, and preferences. No article defined these terms or provided a rationale for the use of a specific term. Many used terms interchangeably.

## Data Presentation

Despite variations in methodology, sampling strategies, and terminology, 3 recurring domains were identified through iterative reading and analysis: knowledge, attitudes, and decision-making of patients and providers. Broadly, knowledge includes efforts to understand the extent to which patients and providers accurately described the risks of antidepressants or untreated depression and anxiety as well as sources of information and access to reliable information. Unique to providers, knowledge includes education, training, and professional engagement.

The domain of attitude is used here to refer to subjective elements such as beliefs, opinions, personal values, emotional experience, concerns, and confidence. Decision-making is used to describe the choices or actions made by participants as well as key influences on those decisions. These overlapping and interrelated domains are not intended to describe discrete phenomena, rather, they are used here to organize the review findings for synthesis, help identify gaps in our understanding, and allow for comparison between patient and providers.

### *Knowledge*

#### Knowledge Assessment

In both patient and provider groups, knowledge was assessed by asking participants about the risks of antidepressants during pregnancy and comparing responses with known teratogenic risk.[29,31,33,42] Overall, responses demonstrated overestimation of the risks of psychopharmacology during pregnancy. No study observed underestimation for this class of medication. Approximately 50% of women thought antidepressant use raised the risk of their child having a major birth defect above the population baseline risk.[42] Many physicians described psychopharmacology as more harmful than other classes of medications.[33] For instance, general practitioners in Denmark overestimated the risk of psychopharmacology, whereas general practitioners and obstetrician-gynecologists in the same sample underestimated the risk of other medications.[29] See Table 2 for greater detail regarding provider knowledge of teratogenic risk.

#### Sources of and Access to Information

Patients named health care providers, community members, and both traditional and social media as important sources of information. Patients rated general practitioners as the most important information source[39] followed by family, significant others, the internet, and media, including traditional and social media sources.[39,44] Obstetrician-gynecologists, radio, television, and magazines were assigned less importance,[39] although some women identified maternal health caregivers (not specified) as trusted sources of guidance.[20,40] Up to 65% of women had used the internet to obtain information.[40,42]

Although patients reported health care providers' opinions as more important than other information sources regarding antidepressants, negative opinions from providers were experienced as distressing for patients, and this distress did not resolve after receiving more reassuring information.[42] Negative information, whether from providers or friends and family, was retained for longer and in more detail than reassuring information.[42] Among women deciding whether to discontinue antidepressants during pregnancy, many endorsed limited access to quality information, or encountered confusing or unclear information, and reported unanswered questions or inadequate time for discussion during treatment planning.[39]

Health care provider education, training, and engagement with the treatment of depression and anxiety during pregnancy, including the use of antidepressants, were assessed in 5 studies.[29,32,33,37,43] Up to 71% of psychiatrists sampled reported some education about psychopharmacology in pregnancy during their training,[37] and between 29% and 56.1% of providers reported they had adequate training related to antidepressant use during pregnancy.[29] Although many health care providers reported interest in more training,[29,37,38] more providers agreed they would personally benefit from additional training than agreed the medical curriculum itself should be amended to include this information.[38] Up to

70.5% of physicians reported reading relevant scientific literature or engaging in additional trainings or conferences on the subject.[33] Previous experience with a specific medication in clinical practice was reported as the primary influence when selecting or avoiding medication.[38] Many health care providers reported encountering incorrect information regarding the safety of antidepressants during pregnancy.[36]

### *Attitudes*

#### Beliefs

Beliefs were collected in 14 studies as spontaneously expressed beliefs or levels of agreement with a provided statement. Patients identified potential for adverse fetal effects as the primary belief affecting decision-making.[20,39,41,44,45] Women named beliefs about the role of a mother to support their decision to decline or continue medication.[44] Personal beliefs about the efficacy of medication, the nature of depression and anxiety, symptom severity, and the potential effects of mood and anxiety symptoms on fetal outcomes impacted decisions.[20,22,39,44] Some patients reported medication would not be preferred to treat depression or anxiety whether pregnant or not[20] or an avoidance of all medication during pregnancy.[45] Patients believed providers were generally not reassuring about medication, and many believed their providers were uncomfortable discussing antidepressants.[42]

Obstetrician-gynecologists expressed their belief that mental health providers are reluctant to prescribe antidepressants during pregnancy, which presents a barrier to mental health care for pregnant individials.[43] They noted that community psychiatrists discharged patients from care or told patients to stop taking medication during pregnancy. This group believed that improved training and increased communication between mental health and perinatal care providers could improve access to mental health care for pregnant people.[43] Health care providers' beliefs about the safety of medication, the risks of untreated depression or anxiety, and their beliefs about patients' preferences are displayed in greater detail in Table 2.

#### Confidence or Concern

Several terms pertaining to confidence in decision-making were used without clear distinction by the authors. These included comfort, confidence, certainty, uncertainty, decisional conflict, concern, and reluctance. Patients reported high levels of uncertainty surrounding treatment decisions. Social stigma, shame, or guilt were named in all studies that examined patient perspectives, and some women feared they would be perceived as unfit parents by health care providers or family.[20,22,34,39,41,42,44,45] Patients had difficulty weighing the relative risks of antidepressants against nontreatment for the woman and for the fetus, which contributed to uncertainty and decisional conflict.[39,41,44] Poor-quality information or limited access to information was associated with higher patient uncertainty in decisions.[39,41,42] Women with more severe symptoms had higher levels of uncertainty, and those with the highest decisional conflict tended to decline antidepressants or defer making a decision, which lead to receiving no treatment.[20]

Among providers, 33.3% to 78.1% of physicians reported some level of confidence in advising patients about antidepressant use during pregnancy.[29,30,32,36,38] Levels of comfort and confidence were related to beliefs about the relative safety of antidepressants. Providers that prescribed antidepressants and those reporting more comfort with prescribing SSRIs were more likely to agree that SSRIs are not associated with increased risk and are relatively safe for use in pregnancy.[30] Those that reported more comfort prescribing SSRIs were more likely to agree that the risks of untreated depression outweigh risk of medications.[30] Although comfort or low levels of concern with prescribing to pregnant patients were reported by many providers, fewer expressed confidence in their own ability to prescribe antidepressants during pregnancy.[29,38]

### *Decision-Making*

Two major categories of decision-making were identified: (1) whether to initiate medication during pregnancy and (2) whether to continue or discontinue medication after pregnancy. The decision to continue medication included whether to maintain or lower the dose or change agents. The decision to discontinue medication included whether to discontinue immediately or by tapering. Medication was discontinued independently by patients or based on provider recommendation. Clinical vignettes were used in 4 studies, one of which included patients, to investigate decision-making; these varied in complexity from a few sentences[35,38] to several narrative paragraphs[34] or were not described in detail.[36]

As many as 68% of women who reported antidepressant use discontinued medication prior to or during their current pregnancy.[39] Whether patients consulted a psychiatrist or obstetric provider did not appear to effect rates of discontinuation.[39] Symptom severity was not consistently identified as a barrier or facilitator to decision-making. Treatment choice did not appear to affect uncertainty, as high to moderate decisional-conflict scores were observed with either choice. However, patients who continued antidepressants endorsed feeling more adequately informed than those who did not.[41] An overall low willingness to use medication during pregnancy was observed among patients with elevated anxiety symptoms.[45]

Among women taking antidepressants prior to pregnancy, feelings of guilt and worry that they were harming their child persisted even after making a decision and despite receiving reassuring information, whether they decided to stop or continue medication.[42,44] Compared with responses of providers, patients reported that concerns related to fetal safety, child development, and breastfeeding were more influential in their decision.[34] Patients also reported that reactions from family, partners, and friends could be supportive or negative of the patient's decision, or absent entirely.[41,44] Approximately 20% received comments from friends, family, coworkers, professionals, or even strangers about the use of antidepressants during pregnancy that were upsetting.[42] Some women reported withholding information from significant others, providers, family, or friends for fear of disapproval.[42,44] Others reported seeking acceptance from providers and significant others to confirm their choice, especially women who took antidepressants during pregnancy.[41,44]

Decision-making patterns were not consistent by provider type or country location. Between 20% and 74% of physicians would avoid starting an antidepressant during pregnancy,[32,35,38] and 24% to 47% would recommend discontinuing once pregnant.[30,32] When determining whether to initiate medication, providers were influenced by patients' mental health treatment history and severity of symptoms. Among providers, *decision-making* also included inquiry as to which specific medication they would choose or avoid based on hypothetical clinical scenarios, described further in Table 2.

Nearly all health care providers reported being influenced by patient preference in treatment options. General practitioners in Australia anticipated more anxiety about the use of antidepressants and predicted higher rates of nonadherence with medication because of patient concerns more often than obstetrician-gynecologists from the same study.[29] Providers appeared to put more emphasis on social stigma during decision-making than patients themselves.[34] Two studies inquired about legal liability and found that 22% of psychiatrists[37] and 55% of general practitioners indicated that liability concerns impacted their decision-making.[36] This concern was more common among providers who discontinue antidepressants during pregnancy (75%) compared with those who would continue (48%).[36]

### Critical Appraisal

Many of the 19 articles share a number of limitations in sampling, design, and data collection. (See Supporting Information: Table S1). A majority of studies relied on convenience sampling. Patients were recruited during clinic visits,[22,39–42,44] from a parent study,[42] through media and advertising,[34] or through an online survey platform.[45] Health care providers were recruited through specific health care systems,[33,34,38,43] listservs,[29,32] professional membership,[30] training workshop,[36] catchment area,[35] or national[31] or regional directories.[31,36,37] Only one study used classic random sampling[30] and 2 used random sampling in combination with alternative strategies.[34,36] No study reported predetermining a sample size through power analysis, pilot data, or other means. Analyses were often limited by sample size and low response rates. Two studies did not achieve a sample size large enough for inferential statistics and were recategorized as qualitative by the authors after data collection.[35,38] Purposeful sampling and recruitment were generally well described.

Key elements of study design were described in a majority of the articles. However, many studies did not include eligibility criteria beyond the identification of a convenience sample. Demographic data were not consistently provided, and most study samples cannot be considered representative. Two studies displayed survey responses in a series of tables that included the survey question.[32,42] However, most studies explained only the general content of surveys without examples or explanation of how the questions were meant to assess the relevant concepts. Confirmation of face validity of the study-specific self-designed survey tools generally was not reported and validity and internal consistency statistics for key instruments were absent from several works.[30–33,35–38] One article used a theoretical framework to inform study design or analysis.[44]

Among the 4 qualitative studies, none commented on researcher reflexivity or the relationship between the researchers and participants or explicitly addressed a framework or criteria used to address qualitative validity. Considering the brevity of the articles, authors presented a balance of exemplars and analysis to provide a vivid representation of participants' experiences and beliefs in 2 studies.[43,44] Within these, the identified themes fit well together and supported the recommendations offered by participants and authors. One grounded theory study was unable to implement theoretical sampling or achieve full saturation.[44] Several mixed-methods studies did not describe either the qualitative or quantitative aims, and analysis or did not address integration of data.[20,22,30,34,41,45]

## DISCUSSION

The aim of this review was to examine the existing literature describing the use of antidepressants during pregnancy from the perspectives of both patients and prescribing providers. The present study expands on previous review[19] of patients' decision-making for antidepressants during pregnancy by including provider perspectives. By including both patients and providers, the results of this review highlight the disparate and sometimes contradictory patterns in the knowledge, attitudes, and decision-making among and between these groups.

Overall, patients reported high levels of distress and uncertainty during decision-making and experienced difficulty accessing quality information. Many were reluctant to discuss the topic with family and friends and believed that their health care providers were not comfortable discussing treatment options. Often, their distress persisted after a decision was made, and patients commonly sought validation for their choice from health care providers and others. Generally, patients and providers shared a tendency to overestimate the risks of antidepressants during pregnancy.

In contrast to the distress and uncertainty reported by patients, many providers endorsed comfort or confidence prescribing antidepressants during pregnancy. Fewer providers reported actually prescribing antidepressants. Many, but not all, providers supported updating training curricula to include more information about these practices, and more believed they would personally benefit from additional training through continuing education.

The results of this review are consistent with a 2018 review of family physicians' perceived role in the treatment of mental health concerns during the perinatal period.[46] Although family physicians recognized their potential role in perinatal mental health, they reported meaningful variations in their preparation, ability, and approaches to treatment decisions. This review further demonstrates variation in the use of evidence-based practices based on provider beliefs, comfort, and inadequate guidance regarding best practices in treatment of depression and anxiety during pregnancy.[24] Clinical reluctance toward psychopharmacology during pregnancy is consistent with the observed practice among neurologists to

continue anticonvulsants and to discontinue by psychiatrists.[47] Wide variations in provider and patient willingness to consider antidepressants during pregnancy suggests pregnant persons are at risk for inadequate treatment of depression and anxiety.

Many studies reviewed here had methodological limitations related to data collection methods, nonrandom samples, poor response rates, and a high potential for bias. Although several qualitative studies explored patient perspectives, a majority of studies concerned with providers' perspectives relied on survey responses. The predominance of data collected through survey-based methods curtails the complexities of actual treatment planning and personal experiences. Self-reported answers may not reflect actual prescribing or adherence patterns, as suggested by low rates of antidepressant use among pregnant individuals.[20]

After careful review of the existing literature, many questions remain. Few studies examined the relationships between knowledge, attitudes, and decision-making. Anxiety was less represented than depression in the literature. No authors compared study results with known prescribing patterns. No explanation was given for incongruent findings such as discrepancies between provider confidence, knowledge, or adherence to evidence-based practice recommendations. There was little knowledge assessment for risks of untreated depression and anxiety. Additionally, no study established what providers might do in the treatment of nonpregnant individuals, and few discussed participants' beliefs regarding antidepressants generally for comparison with perinatal antidepressant use. Finally, although this review includes perspectives of patients and providers, only one article included the perspectives of both and participants were not engaged in treatment planning with one another.

## Limitations

A single investigator made all decisions regarding the inclusion or exclusion, appraisal, and analysis of studies that could have resulted in the omission of relevant articles. A second investigator participated in the study design and interpretation of the review findings. Eligibility was limited to peer-reviewed original research. Therefore, other perspectives are absent, which may be particularly relevant to the views of pregnant people and their families. Although the inclusion of research from multiple countries involving a variety of provider types presents a breadth of perspectives, depth is missing. Furthermore, variation between training and education practices between nations and professions may impact the beliefs and practices of prescribing providers, which could not be assessed here. No study included midwives, and their perspective cannot be described.

## Implications

Pregnant individuals need access to reliable, accurate, and comprehensible information to weigh the individual risks and benefits of antidepressant treatment in pregnancy. As a primary influence on treatment decisions, general practitioners, obstetrician-gynecologists, midwives, nurse practitioners, and mental health providers require the same information.

### *Practice*

During treatment planning, health care providers should be aware that significant others, family, other practitioners, and media may inform patients' decisions. Including family and partners in treatment planning may be useful; however, caution must be taken if these key influencers are in disagreement with the patient and unsupportive of the patient's decision. Providers can also be mindful that patients may be reluctant to bring up the use of antidepressants during pregnancy for fear of social stigma or concern they will be judged unfit parents. Difficulty accessing high-quality information was identified by many patients. Providers can address this is by remaining up to date with current clinical practice guidelines from well-respected sources. Table 3 contains examples of relevant resources for patients and providers.

To increase patients' confidence and minimize uncertainty in treatment decisions, providers should ensure that patients perceive they have had adequate time to discuss options and believe that all their questions were answered. Providers should continue to check-in with patients throughout the pregnancy and not assume that distress has resolved once a patient has accepted or declined an antidepressant. Providers should also be aware that anxiety and distress can delay decision-making and inadvertently deprive a patient of treatment.

Many pregnant patients believe that perinatal care providers are not prepared or able to provide mental health,[17] whereas some obstetrician-gynecologists believe that mental health providers' reluctance to treat patients while pregnant is a primary barrier to care.[43] Efforts to incorporate mental health into standard care, identify the mental health needs of pregnant people through universal screening practices, and facilitate multidisciplinary collaboration between mental health and perinatal care providers could begin to address barriers to treatment. Midwives are well positioned to fully incorporate mental health care during pregnancy into their practice.

### *Policy*

Results of this review show that many health care providers are unaware of current organizational policy or guidelines. Although clear policies and guidelines are important, our results suggest that an emphasis on awareness and promotion of existing guidelines is also necessary. Given that providers are less likely to screen pregnant patients based on individual familiarity with depression and its treatment,[24,46] public health policies are needed to expand the use of universal screening. State and local programming could improve provider familiarity with perinatal depression and anxiety and may increase the identification and subsequent treatment for pregnant individuals. Scarce referral and treatment options could be addressed through license reciprocity and increased telehealth access in areas that lack specialized providers or other resources.

**Table 3. Resources for Patients and Providers**

| Resource | Source |
|---|---|
| Clinical Practice Guidelines | American Psychiatric Association and American College of Obstetricians and Gynecologists (2009 reaffirmed in 2014): https://www.acog.org/-/media/project/acog/acogorg/clinical/files/task-force-report/articles/2009/management-of-depression-during-pregnancy.pdf |
| | British Association for Psychopharmacology Guidelines (2017): https://www.bap.org.uk/pdfs/BAP_Guidelines-Perinatal.pdf |
| Certificate and Continuing Education | Perinatal Mental Health Certificate for Mental Health and Psychotherapy, Psychopharmacology, or Affiliated Professions: https://www.postpartum.net/professionals/certification/ |
| | National Curriculum in Reproductive Psychiatry: https://ncrptraining.org/ |
| | American College of Nurse-Midwives: Advanced Evaluation & Management of Psychiatric Illness in Reproductive Age Women https://www.midwife.org/mental-health-certificate |
| Websites for Patients and Health Providers | Mother to Baby: https://mothertobaby.org/ |
| | Postpartum Support International: https://www.postpartum.net/ |
| | Treating for Two: Medicine and Pregnancy: https://www.cdc.gov/pregnancy/meds/treatingfortwo/treatment-guidelines.html |
| Phone lines | Postpartum Support International Perinatal Psychiatric Consult Line: 1-877-499-4773 (Providers) |
| | Postpartum Support International HelpLine: 1-800-944-4773 (Patients) |

### *Research*

Well-designed studies are needed to develop a deeper understanding of the perspectives of patients and providers, including the potentially unique perspective of midwives, regarding antidepressant use during pregnancy. This work should aim to clarify discrepancies between providers' reported confidence and their adherence to evidence-based practice recommendations, determine understanding of the risks of untreated depression and anxiety, and compare practices for treatment during and outside of pregnancy. Studies that include both patients and providers could help delineate inconsistencies and disagreements between each group's subjective experiences and identify relationship factors that serve as facilitators or barriers to decision-making.

Future research would benefit from clear concept definitions, valid and reliable tools for assessment, and more rigorous quantitative, qualitative, and mixed methodologies. Employing theoretical or conceptual frameworks, such as a cognitive social model for clinical practice behavior that includes environmental factors and personal factors such as education, attitudes, and self-efficacy [48] would help to examine relationships between knowledge, attitudes, and decision-making.

In light of the consistent and ongoing distress experienced by pregnant people considering the use of antidepressants during pregnancy, the results of this review support the use of decision support tools following controlled trials to assesses their efficacy in increasing confidence and reducing distress.[47] Some such aids are currently in development.[49]

### *Education*

The adequacy of treatment planning depends on prescribing providers' knowledge and comfort with psychopharmacology during pregnancy and familiarity with existing evidence-based guidelines. The results of this review highlight variation across provider education experiences and identify a need for updated educational competencies that include education for psychopharmacology during pregnancy for all health care providers who engage with patients during the perinatal period. Providers' responses highlight a preference for continuing education content to supplement their existing knowledge, emphasize current clinical guidelines, and highlight the relative risks of untreated depression and anxiety.[29,37,39,43] Interdisciplinary and interprofessional continuing education can be used to foster collaborative communication between primary, perinatal, and mental health care specialties. Individual organizations can also prioritize the promotion of such trainings.

## CONCLUSION

This review demonstrates variability in the knowledge, attitudes, and decision-making among prescribing providers and pregnant patients as they relate to the use of antidepressants during pregnancy. High levels of distress and uncertainty can delay decision-making and prolong pregnant patients' exposure to untreated depression and anxiety. Concerningly, confidence among health care providers may not correspond with the application of evidence-base practice guidelines, and patients often described providers as uncomfortable or reluctant to discusses these treatments. However, many providers are interested in additional training in this area. Expanding access to both pharmacologic and nonpharmacologic mental health treatment during pregnancy will require a more nuanced examination of patient preferences and needs with an emphasis on minimizing the uncertainty and distress that accompanies decision-making. To foster collaborative treatment

planning that honors patients' preferences and concerns, well-designed studies could help to identify barriers and facilitators in decision-making within the patient-provider relationship by examining the incongruities between patient and provider responses observed in this review.

## ACKNOWLEDGMENTS

The authors would like to acknowledge with gratitude Brynne Campbell Rice, New York University Librarian for Nursing and Allied Health Science, for her guidance in the literature search.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1**. Critical Appraisal: Key Strengths and Weaknesses for 19 Included Articles

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International Journal of Women's Health

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/djwh20

# Depressive symptoms during pregnancy and postpartum in women and use of antidepressant treatment – a longitudinal cohort study

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**To cite this article:** Charlotta Sunnqvist, Karin Sjöström & Hafrún Finnbogadóttir (2019) Depressive symptoms during pregnancy and postpartum in women and use of antidepressant treatment – a longitudinal cohort study, International Journal of Women's Health, , 109-117, DOI: 10.2147/IJWH.S185930

**To link to this article:** https://doi.org/10.2147/IJWH.S185930



Published online: 07 Feb 2019.

International Journal of Women's Health

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ORIGINAL RESEARCH

# Depressive symptoms during pregnancy and postpartum in women and use of antidepressant treatment – a longitudinal cohort study

This article was published in the following Dove Medical Press journal:
*International Journal of Women's Health*

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**Objective:** The aim of this study was to investigate whether women, who reported "symptoms of depression" during pregnancy and up to 1.5 years postpartum, who reported domestic violence or not, were treated with antidepressant medication.

**Patients and methods:** A prospective longitudinal cohort study recruited primi- and multiparous women (n=1,939). The Edinburgh Postnatal Depression Scale (EPDS), the NorVold Abuse Questionnaire, and a questionnaire about medication during pregnancy were distributed and administered three times, during early pregnancy, late pregnancy, and the postpartum period. Antidepressant medication was compared between women with EPDS scores <13 and EPDS scores ≥13 as the optimal cutoff for symptoms of depression.

**Results:** EPDS scores ≥13 were detected in 10.1% of the women during the whole pregnancy, of those 6.2% had depressive symptoms already in early pregnancy and 10.0 % during the postpartum period. Women with EPDS scores ≥13 and non-exposure to domestic violence were more often non-medicated ($P<0.001$). None of the women with EPDS scores ≥13 exposed to domestic violence had received any antidepressant medication, albeit the relationship was statistically nonsignificant.

**Conclusion:** Pregnant women who experienced themselves as having several depressive symptoms, social vulnerability, and even a history of domestic violence, did not receive any antidepressant treatment during pregnancy nor postpartum. This study shows the importance of detecting depressive symptoms during early pregnancy and a need for standardized screening methods.

**Keywords:** antidepressant treatment, depression, domestic violence, postpartum, pregnancy, untreated, reproductive age

## Introduction

Women have an increased risk of experiencing depressive disorders during pregnancy,[1] and the risk is even greater during the postpartum period.[2] A review of the literature has revealed that women who are at high risk, eg, those with experience of lifetime abuse, have a significantly increased risk for depression during both the prenatal and the postpartum period.[3,4] Postpartum depressive symptom has a prevalence of ~16% in Australian population, and the risk factors for developing postnatal depression include a history of depression before and/or during pregnancy, dysfunctional partner relationship, multiple stressful life events, low social support, low income, and fewer years of education.[5] In addition, Finnbogadóttir and Dykes[6] showed that symptoms of depression both during pregnancy and up to 1–1.5 years postpartum were associated with domestic violence. Untreated postpartum depression might negatively affect

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http://dx.doi.org/10.2147/IJWH.S185930

the interaction between mother and child, for example, by reducing sensitivity and availability to the needs of the infant.[4] In Sweden, there is no general praxis at the Antenatal Care (ANC) units regarding screening for depression during pregnancy. At the Child Welfare Centers (CWC), however, mothers at 6–8 weeks postpartum are screened for postnatal depression with the Edinburgh Postnatal Depression Scale (EPDS).[7]

Several studies have found that intimate partner violence (the most frequent type of domestic violence) is significantly associated with both prenatal and postnatal depression.[3,4] The presence of severe symptoms of depression detected in early pregnancy,[8] late pregnancy,[6] and postpartum[6] may be a predictive factor for exposure to domestic violence. Thus, not only is untreated depression during pregnancy and postpartum a major risk factor for both mothers' and infants' health, but depressive symptoms may also be a result of previous and/or present exposure to domestic violence.[6,8] The treatment of pregnant women with depression is complex and requires both evaluation of risks and benefits, and most pregnant women with depression do not get treatment despite devastating effects on women, infants, and families.[9] A systematic review from 2015 found that untreated depression could lead to adverse effects on the developing fetus, such as hyperactivity or irregular fetal heart rate and increased rates of premature deaths and neonatal intensive care admissions in newborns.[10] Also, women with a history of depression who discontinue antidepressant treatment during pregnancy are at much higher risk of relapse than those who continue their medication. Previous studies have found that antidepressant medical treatment drops from 70% to 27% during pregnancy, and most women do not receive further treatment beyond 6 weeks of gestation.[10] There is evidence that pregnant women with major depressive disorder require medical therapy[11] and psychotherapy for mild and moderate depressive disorders.[12] According to a review by O'Connor et al,[12] the absolute risk of antidepressant during pregnancy appear to be small, and cognitive behavioral therapy may be an effective alternative treatment approach for mild and moderate depressive disorders. Results from a previous longitudinal study showed that severe symptoms of depression were associated with domestic violence.[6] The distressing situation, being exposed to domestic violence and having a depression weakens the mother's ability to take care of her newborn child and, therefore, an antidepressant treatment may be helpful for the mother to cope with this vulnerable situation. A woman who is depressed in pregnancy faces the difficult process of weighing the pros and cons of starting antidepressant treatment.[13] However, clinicians and patients should carefully and individually weigh maintenance therapy against the small possible risk of neurodevelopmental problems suggested by the currently available literature.[14] Therefore, there is a need to explore depressive symptoms and the prevalence of antidepressant medication in the high-risk group of pregnant women who are exposed to domestic violence.

The aim of this study was to investigate whether women, who reported "symptoms of depression" during pregnancy and up to 1.5 years postpartum, with or without exposure to domestic violence, were treated with antidepressant medication.

## Patients and methods

The present study is a cohort study with a longitudinal design and a part of a larger project, Pregnant Women and New Mothers' Health and Life Experience, where the cohort consisted of 1,939 pregnant women, recruited in early pregnancy, in gestational week 13 (mean 12.8, SD ±5.11).[8] The inclusion criteria were both primi- and multiparous women ≥18 years of age, registered at ANC when pregnant, and who could understand and write Swedish or English. The recruitment to the study occurred between March 2012 and September 2013 in a multicultural area in the southwest of Sweden, and data collection continued until the end of April 2015. The population comprises of all listed pregnant women at 17 ANCs situated in the multicultural city (n=7), the University City (n=4), and smaller municipalities (n=6). Also, one ANC providing specialized care for complex pregnancies such as women with diabetes and one for women with history of drug abuse in need of extra support were also included. Four of the ANCs were private care facilities. At the time for recruitment, the participants were fully informed about the purpose of the study. They received verbal and written information about the study from their midwife and were invited to respond to the questionnaires in a private place at the ANC facility. The women were promised confidentiality, and they were encouraged to feel free to disclose whether they were living in a violent relationship. Professional help was provided for those respondents who came forward and asked for help. The participants were requested to answer three questionnaires, ie, on two occasions during pregnancy at their ANC (Q-I and Q-II) and once 1–1.5 years postpartum at their CWC (Q-III). The total cohort comprised 1,939 women and they completed the first questionnaire (Q-I) in "early pregnancy". The second questionnaire II was completed at gestational week 34 or in "late pregnancy" (mean 33.9, SD ±2.20 weeks), with a response rate of 78.8% (N=1,527),

and the final questionnaire III (Q-III) was completed at the end of April 2015 by 37.2% (N = 732) women who who visited their CWC 1–1.5 years postpartum (Figure 1).[6]

## Questionnaires

The questionnaires consisted mainly of four validated instruments. The EPDS is intended to screen risk of depression in the postnatal period but may also be used during pregnancy.[15] The EPDS detects common symptoms of depression and consists of ten items. Each item is rated from 0 to 3, with higher scores indicating more perceived symptoms of depression. The participants were requested to rate each statement with regard to how they had felt during the past 7 days (Q-I–III). The cutoff score for depression was originally set at 12/13.[15] The EPDS has a 72% sensitivity and 88% specificity for women postpartum but has a lower degree of detection for depression in pregnancy.[16] The EPDS was validated on a Swedish community sample against criteria for major depression according to the DSM-III-R.[17] We chose the cutoff score to be 13.

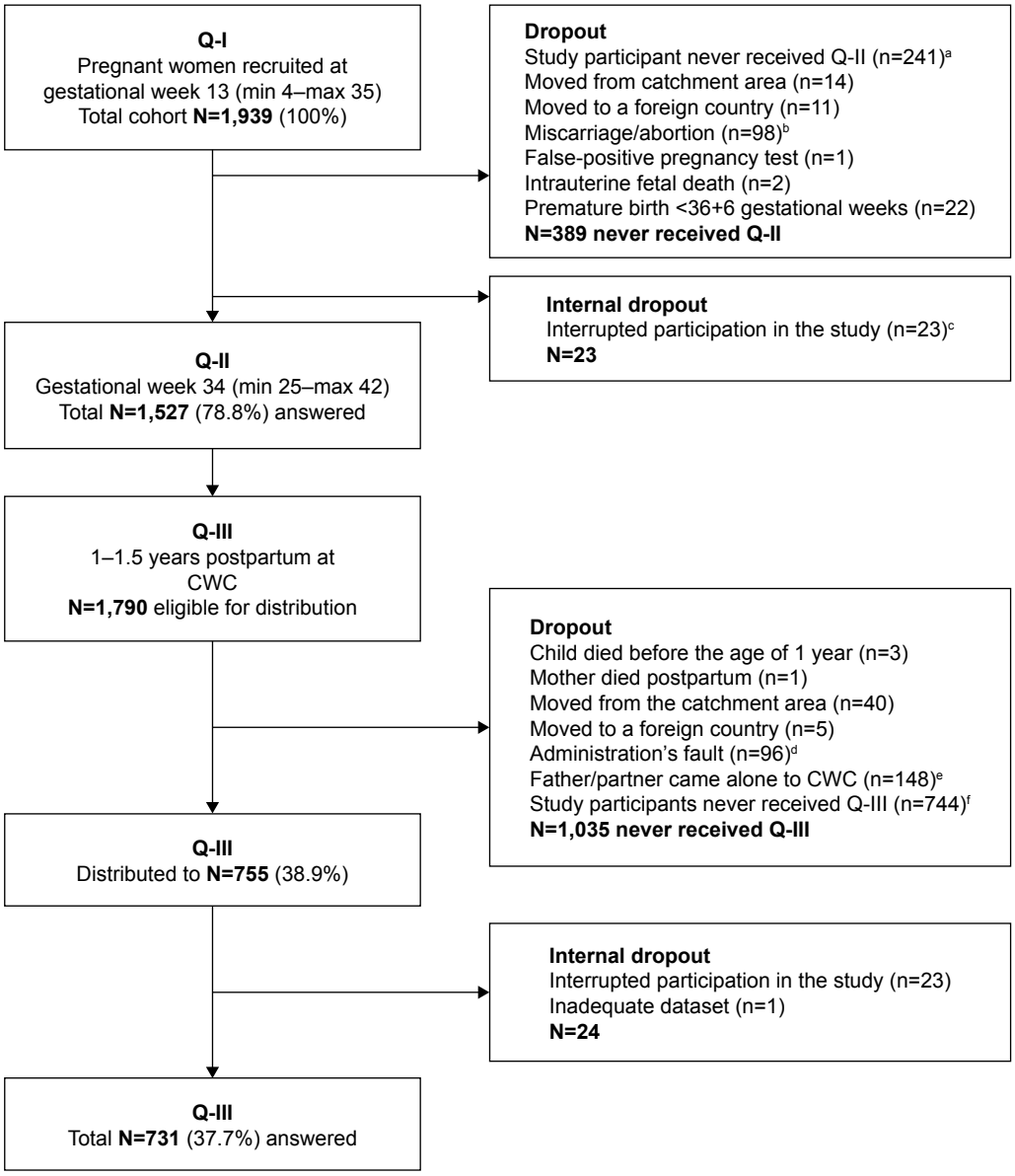


**Figure 1** Flowchart of the distributed and received answers for Q-I–III.[6]

**Notes:** [a]The midwives forgot to give Q-II to the study participants (n=239), and there were instances of missing consent (n=2). [b]Spontaneous and legal abortions (n=84), missed abortions (n=4), spontaneous and legal abortions due to malformations or for personal reasons >18 gestational weeks (n=10). [c]Offered no explanation or did not understand the questions about violence well enough or had difficulties with the language. Also, the participant was too stressed to stay to complete the questionnaire (n=3). [d]Q-III not delivered to the right CWC, women had changed CWC, wrongly registered civic registration number (rarely), difficult to track because the baby was born out of the catchment area or at home, and CWC-nurse did not give the study participant the Q-III because the partner accompanied the woman. [e]Inclusion criteria not fulfilled. [f]The nurses at CWC forgot to give Q-III to the study participants.

**Abbreviations:** CWC, Child Welfare Centers; Q-I, Questionnaire I; Q-II, Questionnaire II; Q-III, Questionnaire III.

The Alcohol Use Disorders Identification Test (AUDIT)[18] was used at each time of questionnaire administration (Q-I–III). The first item of the AUDIT concerns the frequency of drinking alcohol. The given answers were "never" or the amount of beverage consumption.

The NorVold Abuse Questionnaire (NorAQ)[19] was the main instrument used to investigate emotional, physical, and sexual abuse and level of experienced violence for <18 years of age (during childhood) and ≥18 years of age (adulthood) and is designed for use in and validated in Nordic countries.[19] A modified question from the Abuse Assessment Screen[20] was used to investigate current partner abuse during pregnancy by answering yes/no, and if yes "by whom".

One question regarding the pharmacological treatment the women had used during the last year was included in all three questionnaires with the purpose of covering the time period before pregnancy, during pregnancy, and postpartum. The pharmacological treatment alternatives were the following: sleeping pills, pain relievers, antidepressants, sedatives, amphetamine, cocaine, or other psychotropic street drugs. All alternatives were rated as follows: never, occasionally, short period, long period, and all the time. In this study, only the use of antidepressant drugs was analyzed.

## Definitions

Domestic violence was defined according to WHO's definition as physical, sexual, psychological or emotional violence, or threats of physical or sexual violence that are inflicted on a pregnant woman by a family member, ie, an intimate male partner, marital/cohabiting partner, parents, siblings, or a person very well known to the family, or a significant other (ie, former partner), when such violence often takes place in the home.[21]

A history of violence was defined as a lifetime experience of emotional, physical, or sexual abuse occurring during childhood (<18 years), adulthood (≥18 years), or both, regardless of the level of abuse or the perpetrator's identity, in accordance with the operationalization of the questions in the NorAQ.[21] Also, we used the definitions determined by Swahnberg and Wijma et al[19] for severity of abuse, which classifies abuse as mild, moderate, or severe, and the type of abuse used. Any level of any type of violence was regarded as being exposed to violence.

## Classification of the sociodemographic variables and medication

The sociodemographic variables used in this study are shown in Table 1.

Three age groups were created: 18–25, 26–34, and ≥35 years, and language was selected as Swedish or a foreign language spoken at home. Cohabiting status was dichotomized as being single/living apart or as cohabitant/married. Educational status was divided into two groups: low educational status, ie, basic education and high school, and high educational status, ie, above high school, including university. Employment status was dichotomized as being employed (including parental leave and studying) or unemployed (sick leave). Financial distress was dichotomized as "no" (no problem) or "yes" (serious financial distress). Smoking/using wet tobacco was dichotomized as "yes" or "no", ie, yes, if the woman was a daily smoker or wet-tobacco user at some point during pregnancy, and no, if never smoked or used wet-tobacco or stopped before pregnancy. Alcohol consumption was dichotomized as "yes" (at least once a month) or "no" (never). For antidepressant medication, the answers were classified as "no medication", "medication in periods", and "constant medication".

## Statistical methods

All data were based on the women's answers from the questionnaires (Q-I, Q-II, and Q-III). Descriptive statistics were used to show the prevalence and percent of depressive scores during early and late pregnancy, as well as 1–1.5 years postpartum. Chi-square analysis was used to investigate differences in sociodemographic and lifestyle factors in early pregnancy in relation to depressive symptom scores. The variable for depression was computed based on the sum of EPDS scores, ie, symptoms of depression during pregnancy or postpartum, whereby an optimal cutoff of ≥13 was chosen as representing the presence of symptoms of depression. Women who did not report any depressive symptoms at all were analyzed as a separate group (n=130). There were no differences in sociodemographic characteristics between those with a score of zero and those with a score of 1–12 on EPDS, and, therefore, the EPDS variable was dichotomized as EPDS scores <13 or ≥13. Statistical significance was considered at $P<0.05$ (two-tailed). Statistical analyses were performed using the SPSS version 22.0 for Windows.

# Ethics approval and informed consent

The research was conducted according to the principles stated in the World Medical Association Declaration of Helsinki[41] and the WHO's ethical and safety recommendations for research on violence against women.[42] Written informed

**Table 1** Comparison of sociodemographic background and lifestyle factors in early pregnancy in relation to EPDS score (N=1,939)

| Characteristics | EPDS 0 | EPDS 1–12 | EPDS ≥13 | Total[a] | *P*-value ($\chi^2$) |
|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | |
| | 130 (6.9) | 1,572 (83.8) | 175 (9.3) | 1,747 (100) | |
| Age in years[b] | | | | | 0.006 |
| 18–25 | 16 (12.4) | 265 (17.1) | 43 (24.9) | 308 (17.9) | |
| 26–34 | 87 (67.4) | 986 (63.6) | 112 (64.7) | 1,098 (63.7) | |
| ≥35 | 26 (20.2) | 300 (19.3) | 18 (10.4) | 318 (18.4) | |
| Missing in analysis n=215 | | | | | |
| Language | | | | | 0.008 |
| Swedish | 107 (82.9) | 1,208 (77.0) | 119 (68.4) | 1,327 (76.2) | |
| Foreign language | 22 (17.1) | 360 (23.0) | 55 (31.6) | 415 (23.8) | |
| Missing in analysis n=197 | | | | | |
| Cohabiting status | | | | | <0.001 |
| Single/living apart | 2 (1.6) | 67 (4.4) | 26 (14.9) | 93 (5.5) | |
| Common law spouse/married | 118 (93.7) | 1,454 (95.6) | 148 (85.1) | 1,602 (94.5) | |
| Missing in analysis n=244 | | | | | |
| Educational status | | | | | <0.001 |
| Low educational status | 42 (32.3) | 491 (31.2) | 81 (46.3) | 572 (32.7) | |
| High educational status | 88 (67.7) | 1,081 (68.8) | 94 (53.7) | 1,175 (67.3) | |
| Missing in analysis n=192 | | | | | |
| Employment status | | | | | <0.001 |
| Employed | 124 (95.4) | 1,500 (95.5) | 148 (84.6) | 1,648 (94.4) | |
| Unemployed | 6 (4.6) | 71 (4.5) | 27 (15.4) | 98 (5.6) | |
| Missing in analysis n=193 | | | | | |
| Financial distress | | | | | <0.001 |
| No | 81 (62.3) | 838 (53.4) | 62 (35.4) | 900 (51.6) | |
| Yes | 49 (37.7) | 732 (46.6) | 113 (64.6) | 845 (48.4) | |
| Missing in analysis n=194 | | | | | |
| Smoking/wet tobacco | | | | | 0.003 |
| No | 110 (87.3) | 1,239 (90.8) | 126 (72.4) | 1,365 (80.4) | |
| Yes | 16 (12.7) | 284 (18.6) | 48 (27.6) | 332 (19.6) | |
| Missing in analysis n=242 | | | | | |
| Use of alcohol | | | | | 0.339 |
| No | 65 (52.4) | 698 (46.1.1) | 85 (48.9) | 783 (46.4) | |
| Yes[c] | 59 (47.6) | 816 (53.9) | 89 (51.1) | 905 (53.6) | |
| Missing in analysis n=251 | | | | | |

**Notes:** Statistical significance accepted at $P<0.05$, Pearson's Chi-square two-tailed analysis was used for statistical differences between EPDS scores. [a]Missing in the analysis for EPDS, n=62. [b]Age in early pregnancy, at the time of recruitment. [c]At least once in a month.
**Abbreviation:** EPDS, Edinburgh Postnatal Depression Scale.

consent was obtained before the participants received their first questionnaire. The participants were informed about the law of Swedish Data Inspection. All questionnaires were collected and coded by the third author and were kept in a locked safe. Approval for the study was obtained from the Regional Ethical Review Board where this study took place (Dnr: 640/2008).

## Results

Women with scores of depressive symptoms (EPDS scores ≥13) compared to women with EPDS scores <13, were significantly younger, more often speaking a foreign language at home, single/living apart, less educated, unemployed, financially distressed, and smokers (Table 1).

### Prevalence of depressive symptoms

The prevalence of depressive symptoms (EPDS scores ≥13) were in early pregnancy (Q-I) 9.3%, in late pregnancy 8.2% (Q-II), and 10.0% postpartum up to 1.5 years (Q-III) (Table 2).

In early pregnancy (Q-I), 9.3% (n=175) of the women reported scores of depressive symptoms (EPDS score ≥13), and 69.1% (n=121) of them reported it only in the early pregnancy. Almost 34% (n=59) reported scores of depressive symptoms (EPDS score ≥13) only in late pregnancy (Q-II), and 22.7% (n=38) both in early and late pregnancy, but not postpartum. Amply 5% (n=9) reported scores of depressive symptoms (EPDS score ≥13) in late pregnancy as well as postpartum, and additionally 5.1% (n=9) had high scores at

**Table 2** Prevalence of depressive symptoms in a cohort of pregnant women with EPDS score <13 or ≥13 until 1–1.5 years postpartum (N=1,939)

| Characteristics | Early pregnancy Q-I | Late pregnancy Q-II | 1–1.5 years postpartum Q-III |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Total in analysis | 1,877 (100)[a] | 1,425 (100)[b] | 665 (100)[c] |
| EPDS score <13 | 1,702 (90.7) | 1,310 (91.8) | 599 (90.0) |
| EPDS score ≥13 | 175 (9.3) | 115 (8.2) | 66 (10.0) |

**Notes:** [a]Q-I, 62 missing participants. [b]Q-II, 102 missing participants. [c]Q-III, 66 missing participants.
**Abbreviations:** EPDS, Edinburgh Postnatal Depression Scale; Q-I, Questionnaire I; Q-II, Questionnaire II; Q-III, Questionnaire III.

all three time points of measures. Total 14.6% (n=284) of the study participants (n=1,939) reported scores of depressive symptoms (EPDS score ≥13) one or more times during pregnancy and/or up to 1.5 years postpartum.

## Women exposed and nonexposed to domestic violence

Women with no history of domestic violence and with scores of depressive symptoms were significantly more often non-medicated ($P<0.001$) compared to women with scores under cutoff of depressive symptoms (EPDS score <13), throughout the study (Q-I–III). Among women exposed to domestic violence with scores of depressive symptoms (EPDS score ≥13) throughout the study (Q-I–III) were more often non-medicated compared to women with under cutoff scores of depressive symptoms (EPDS score <13), but these results did not reach statistical significance (Table 3).

## The group of women with scores of depressive symptoms and antidepressant medication

During pregnancy (Q-I and Q-II), 10.1% of women belonged to the group with scores of depressive symptoms (EPDS score ≥13), and of those women, 6.2% had scores of depressive symptoms (EPDS score ≥13) already at the first visit at ANC. The prevalence of women with scores of depressive symptoms (EPDS score ≥13) and no antidepressant medication during pregnancy was 10.8% (n=190) (exclusively presented in the text).

During early pregnancy (Q-I) and late pregnancy (Q-II), the majority of women with scores of depressive symptoms (EPDS score ≥13) who had been exposed to domestic violence did not receive antidepressant medication (80% and 85.7%, respectively). At postpartum (Q-III), none of the women with scores of depressive symptoms (EPDS

**Table 3** Women exposed or nonexposed to domestic violence, EPDS scores, and antidepressant medication during early pregnancy until 1–1.5 years postpartum (N=1,939)[a]

| Characteristics | Total n (%) | Q-I | | P-value ($\chi^2$) | Total n (%) | Q-II | | P-value ($\chi^2$) | Total n (%) | Q-III | | P-value ($\chi^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | EPDS <13 n (%) | EPDS ≥13 n (%) | | | EPDS <13 n (%) | EPDS ≥13 n (%) | | | EPDS <13 n (%) | EPDS ≥13 n (%) | |
| EPDS score | 1,751 (100) | 1,591 (100) | 160 (100) | df 2 | 1,310 (100) | 1,209 (100) | 101 (100) | df 2 | 587 (100) | 531 (100) | 56 (100) | df 2 |
| DV | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| No medication | 1,616 (93.2) | 1,501 (94.8) | 115 (76.7) | <0.001 | 1,211 (93.4) | 1,136 (94.4) | 75 (79.8) | <0.001 | 525 (93.1) | 486 (94.4) | 39 (79.6) | <0.001 |
| Not taking oral medication regularly as prescribed | 51 (9.9) | 33 (2.1) | 18 (12.0) | | 36 (2.8) | 26 (2.2) | 10 (10.6) | | 12 (2.1) | 7 (1.4) | 5 (10.2) | |
| Regularly taking oral medication as prescribed | 66 (3.8) | 49 (3.1) | 17 (11.3) | | 50 (3.9) | 41 (3.4) | 9 (9.6) | | 27 (4.8) | 22 (4.3) | 5 (10.2) | |
| Yes | | | | | | | | | | | | |
| No medication | 16 (88.9) | 8 (100) | 8 (80.0) | 0.294 | 12 (92.3) | 6 (100) | 6 (85.7) | 0.538 | 20 (87.0) | 13 (81.3) | 7 (100) | 0.316 |
| Not taking oral medication regularly as prescribed | 0 (0.0) | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | | 1 (4.3) | 1 (6.3) | 0 (0.0) | |
| Regularly taking oral medication as prescribed | 2 (11.1) | 0 (0.0) | 2 (20.0) | | 1 (7.7) | 0 (0.0) | 1 (14.3) | | 2 (8.7) | 2 (12.5) | 0 (0.0) | |

**Notes:** Statistical significance accepted at $P<0.05$, Pearson Chi-square two-tailed analysis was used for differences between EPDS score and antidepressant medication as well as DV. [a]Missing information for 307 women in Q-I, 217 in Q-II, and 144 in Q-III.
**Abbreviations:** DV, domestic violence; EPDS, Edinburgh Postnatal Depression Scale; Q-I, Questionnaire I; Q-II, Questionnaire II; Q-III, Questionnaire III.

score ≥13) exposed to domestic violence had received antidepressant medication (100%) (Table 3).

## Discussion

We found that all women exposed to domestic violence with scores of depressive symptoms throughout pregnancy and postpartum were untreated with antidepressant medication. We also found that nonexposed women, with scores of depressive symptoms, were barely treated with antidepressant medication. Despite known risk factors for depression, such as, psychosocial vulnerability and ongoing or previous exposure to domestic violence, these risk factors did not lead to clinical identification.

We chose to study maternal depressive symptoms on two occasions during pregnancy and on one occasion during postpartum, ie, 1.5 years after birth. It has been found that perinatal depression occurs during pregnancy or in the first 12 months after birth and is one of the most common medical complications during pregnancy.[22] In a review by Goodman,[23] postpartum depression occurs within the first couple of weeks after giving birth, but for some women, the symptoms of depression occur later during the first postpartum year. The symptoms of depression may continue for 2 years after giving birth.[23]

A limitation in the study design was that no clinical assessment of depression could be performed, and, therefore, it is unknown whether the study participants would meet the diagnostic requirements for clinical depression. Thus, the women in the group with symptoms of depression were those with EPDS scores ≥13. Screening with EPDS is valuable but unfortunately not sufficient, because semi-structured interviews would be needed to confirm a diagnosis of depression. Nevertheless, according to Statens Beredning för Medicinsk Utvärdering [Swedish Agency for Health Technology Assessment and Assessment of Social Services],[16] EPDS has the advantage of being able to detect several women with depressive symptoms. In addition, the data offer no information if the respondents have been offered or undertaken psychological treatment for depressive symptoms. Furthermore, there was a nonsignificant trend between the report of domestic violence and untreated depression, which may be caused by a lack of power. This in turn may be the result of the well-known difficulties in reporting domestic violence.

The strength of the current study is the large sample size as well as the use of a well-defined cohort. This longitudinal study, based on prospective data, allowed for comparison between those who had more symptoms of depression and those who did not. However, the risk of dropout over time in this type of study is well known and was present in the current study. Another strength was the use of validated instruments included in the questionnaires used.[15,19]

In this study, women who had symptoms of depression also had less favorable sociodemographic and life-style factors. They were younger, single or living apart from the father, had lower educational level, were unemployed, had more financial distress, were smokers, and spoke a foreign language at home. It has been shown that female gender, living alone, having less education, and with previous childhood traumas were risk factors for depression and suicide attempts.[24] A recent systematic review showed that the most significant factors associated with antenatal depression or anxiety were lack of partner or social support and history of abuse or domestic violence.[25] In addition, some studies show that the offspring of women who experienced significant psychosocial stress already during pregnancy, have an increased risk of later neuropsychiatric illness,[26,27] especially, when untreated.[28] Children of these vulnerable mothers also may be extra vulnerable right from birth.[29]

We also found that women with symptoms of depression, besides being socially vulnerable, also had a risk factor in having been exposed to domestic violence. Previous study has shown a clear association between exposure to domestic violence during early pregnancy as well as in late pregnancy and symptoms of depression.[6] Obstacles to early recognition of current or previous exposure to violence may be the lack of local guidelines and lack of available support. Midwives may lack the confidence or knowledge about this matter and furthermore may fear the perpetrator.[30] Since 2014, the National Board of Health and Welfare in Sweden has recommended that all women attending ANCs when pregnant should be asked about any experience of violence.[31] Nearly 80% of all pregnant women in Sweden were asked about any experience of violence at their ANC during the year 2014.[32] However, screening for symptoms of depression is not a routine until 6–8 weeks postpartum at CWCs. It would have been wise to screen for depressive symptoms at the same time as pregnant women were asked about their experience of violence. Another obstacle was the survivors' fear of authorities and that the social welfare department would take their children from them if they disclosed a violent relationship.[30] All in all, to be exposed to domestic violence as well as having symptoms of depression when pregnant is a complex issue, and there is a need of good cooperation between the different health care providers as well as social welfare authorities to ensure the best outcome for the mother-to-be and the unborn infant's health.

Several studies concerning the general population have shown that only a minority of the depressed patients had received adequate antidepressant therapy before fatal outcome.[33] Depression is the most common mental disorder worldwide and is the primary cause of suicide and long-term suffering;[2] the lifetime prevalence in women is almost 50%.[34] Maternal suicide attempts and suicide are the most serious complications to depression in the perinatal and postnatal time periods.[35] Moreover, untreated depression during pregnancy has also been related to lower intellectual and cognitive abilities among offspring,[28] and in a recent systematic review and meta-analysis, evidence was found that untreated depression was associated with a significantly increased risk of preterm birth and low birth weight. Furthermore, it has been found that infants born to depressed mothers were admitted to neonatal intensive care twice as often and had a shorter duration of breastfeeding than nondepressed mothers.[11] Several studies have reported that depressed mothers are not able to provide the loving and consistent care that the child needs, which has a negative impact for mother and infant attachment.[11,36]

There is an ongoing debate regarding treatment with antidepressants during pregnancy since antidepressant medication is able to pass through the placental barrier and, therefore, may pose a risk for adverse fetal development.[37,38] Nulman et al[28] found that there was no deviance in neurodevelopment among offspring to mothers receiving selective serotonin reuptake inhibitors (SSRIs) during pregnancy compared to siblings. However, Brandlistuen et al[39] found a relationship among siblings exposed to SSRIs prenatally and anxiety at 36 months, compared to a nonexposed sibling. Anxiety was specific and not related to other behavioral problems in the child. Unfortunately, there are no controlled, randomized trials regarding the use of antidepressants in pregnancy, and according to a review from 2014,[40] there is lack of evidence from good quality studies that clinicians and patients should refrain from the initiation of SSRI treatment during pregnancy or that such treatment should be discontinued. However, clinicians and patients should carefully and individually weigh maintenance therapy against the small possible risk of neurodevelopmental problems suggested by the currently available literature.[40]

## Conclusion

This study supports the importance of detecting risks for maternal depression in a standardized manner already during early pregnancy. For pregnant women who reported several depressive symptoms and social vulnerability with a history of domestic violence, these risk factors did not lead to clinical identification nor to any antidepressant treatment during pregnancy or postpartum. The findings show the clinical challenge in detecting this important group of women during an especially vulnerable time in their life. The need for standardized screening methods for depression both during pregnancy and postpartum is emphasized.

## Acknowledgments

The authors would like to thank all the midwives who conducted the recruitment as well as all the CWC nurses who helped with the administration of the postpartum questionnaire. Special thanks go to Lars Wahlgren for his excellent statistical support. The Swedish Crime Victim Compensation and Support Authority contributed with funding for this research (Dnr 09082/2014; Dnr 09097/2015).

## Author contributions

HF conceived the study and performed the collection of the data, and all authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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